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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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THE NEW YORK ACADEMY
OF MEDICINE

JUNE 1941

UTILIZATION OF SELECTIVE MICROBIAL AGENTS IN THE STUDY OF BIOLOGICAL PROBLEMS

Harvey Lecture, March 21, 1940

RENÉ J. DUBOS

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ON THE third of August, 1857, Pasteur presented before the Scientific Society of Lille the first of his studies on the microbial theory of fermentation, "Mémoire sur la fermentation appelée lactique." On this occasion, he expressed his belief that, for each type of fermentation, one would find a specific ferment, characterized not only by its morphology and resistance to inhibitory substances, but also by its specific behavior as a chemical agent.[1]

On December 21st of the same year, Pasteur announced, at the end of his memoir on alcoholic fermentation, that he had observed a new "mode of fermentation" which attacked the *d*-form of tartaric acid, but which was inactive against the *l*-form;[2] experimental details concerning this observation were presented on March 29, 1858;[3] again in 1860 Pasteur described that a mold, *Penicillium glaucum*, exhibited the same specific behavior toward tartaric acid, attacking the *d*-form and not the *l*-form.[4] He pointed out that this selective fermentation afforded an

easy technique for the separation of the *l*-tartaric acid from the racemic mixture, and that the method would probably be applicable to the separation of other isomers. He also emphasized that since "the character of dissymmetry of organic compounds can modify the chemical reactions of physiological order," the phenomenon of specificity which he had observed was probably of great biological significance.

The very beginnings of experimental microbiology thus demonstrated the specific character of the biochemical reactions induced by microörganisms, and suggested to biochemists and physiologists new techniques and new problems. It is hardly necessary to state that bacterial physiology has repeatedly confirmed Pasteur's views on the part played by microbial life in the economy of natural processes. If organic matter does not accumulate in nature, it is because countless species of microörganisms hydrolyze it, oxidize it and eventually break it down to carbon dioxide, ammonia, water, and mineral salts. We know furthermore that, under natural conditions, each one of these microbial species is adapted to the performance of a limited, well-defined biochemical task. One may illustrate this statement by recalling the discovery of bacteria whose sole source of energy is the oxidation of ammonia to nitrites, of others which oxidize nitrites to nitrates, of still others which convert elementary sulfur to sulfuric acid, etc. Several species of bacteria which readily decompose cellulose fail to attack cellobiose or glucose; there are microörganisms which oxidize hydrogen, methane, petroleum, phenol, formol, etc. In fact, it can be stated that one can find in nature, in soil or water for instance, microörganisms capable of performing almost every possible type of biochemical reaction, many of which are not known to take place in the animal or the plant kingdoms. In many cases, the catalysts responsible for these reactions have been extracted from the microbial cells, and have been found to exhibit a remarkable specificity. Because of their cellular origin, these catalysts are able to operate under physiological conditions (pH, temperature, etc.) and this property, together with their specificity, renders them ideal reagents for the analysis of biological problems.

It is apparent, therefore, that given enough time, patience, and skill, the bacteriologist can discover in nature microbial reagents adapted to the study of a great variety of biological problems. The few examples which will be considered in the following discussion have been investigated at the Hospital of the Rockefeller Institute; they have been se-

lected because, in each case, new bacterial species were isolated from soil and active catalysts prepared from cultures of these organisms, in an attempt to discover reagents useful in the study of clinical problems under investigation in our hospital. It is perhaps justifiable, therefore, to emphasize that the facts here reported are not chance findings, but are illustrations of a method which has a distinguished past in bacteriological chemistry and which deserves the consideration of physiologists and biochemists.

The decomposition of creatinine by bacterial enzymes. In the course of studies on renal function, it became necessary to develop a method for the quantitative estimation of the very small amounts of creatinine present in blood. The identification and analysis of creatinine in tissues and biological fluids have chiefly depended on colorimetric methods which are so unspecific that many authors have denied the very presence of creatinine in the circulating blood.

It was in an attempt to develop analytical methods specific for creatinine that several species of bacteria capable of attacking this compound were isolated from soil.[5] Two of these bacterial species have been studied with some care; when grown in the proper medium, they have yielded enzyme systems in the form of resting cells which are capable of decomposing creatinine in the absence of bacterial growth. These enzyme systems exhibit a remarkable specificity.

Table I illustrates the effect of the enzyme prepared from the "NC" culture upon a number of substances which give the Jaffe reaction (one of the color tests most commonly used to detect the presence of creatinine). It is clear that, of the Jaffe reactive compounds which were tested, only creatinine was rapidly decomposed. The addition of one methyl group to the creatinine molecule completely inhibited enzymatic activity, and the mere shift of the methyl group from position 3 (in creatinine) to position 5 (in 5-methylglycocyamidine) diminished the rate of decomposition very greatly. Acetyl creatinine and glycocyamidine were also slightly decomposed.

The "NC" enzyme preparation was also tested against a number of substances very closely related to creatinine but which do not give the Jaffe reaction with alkaline picrate. In these cases, the activity of the enzyme was tested by the determination of a characteristic product of the reaction. Urea was selected since it was found to be the most constant product of the action of the NC enzyme upon creatinine.

TABLE I

DECOMPOSITION BY NC ENZYME OF JAFFE-REACTIVE SUBSTANCES RELATED TO OR ASSOCIATED WITH CREATININE

(Reprinted from the *Journal of Biological Chemistry*)

COMPOUND*	PERCENTAGE DECOMPOSITION MEASURED BY CHANGE IN JAFFE REACTION
	per cent
Creatinine	100
5-Methylcreatinine	0
Dimethylcreatinine	0
† Acetylcreatinine	10†
4-(or 5-) Benzoylcreatinine	0
5-Benzylcreatinine	0
2-Benzylcreatinine	0
Glycocyamidine	10
5-Methylglycocyamidine	10
Hunter's chromogenic substance in human erythrocytes	0

* The nomenclature is that used by Greenwald (1925).

† Acetylcreatinine does not undergo further destruction when the incubation is prolonged. This is different from the action with glycocyamine and 5-methylglycocyamidine, since both these compounds may be completely decomposed if the incubation is continued for some hours.

TABLE II

PRODUCTION OF UREA BY ACTION OF NC ENZYME UPON NON-JAFFE-COMPOUNDS RELATED TO CREATININE

(Reprinted from the *Journal of Biological Chemistry*)

COMPOUND	PRODUCTION OF UREA*
Creatinine	+
Creatine	+
Methylhydantoin	0
Methylhydantoic acid	0
Hydantoin	0
Guanidineacetic acid	+
Methylguanidine	+
Arginine	+
Sarcosine	0
Guanidine	Trace

* + indicates the production of approximately equivalent amounts of urea.

TABLE III

ACTION OF "HR" ENZYME PREPARATION ON COMPOUNDS RELATED TO CREATININE

(Reprinted from the *Journal of Biological Chemistry*)

COMPOUND	PERCENTAGE DECOMPOSITION MEASURED BY JAFFE REACTION
	per cent
Creatinine	100
5-Methylcreatinine	0
4- (or 5-) Benzoylcreatinine	0
5-Benzylcreatinine	0
2-Benzylcreatinine	0
Diamethylcreatinine	0
5-Methylglycocyamidine	0
Glycocyamidine	15

The results presented in Table II indicate that creatine, guanidine-acetic acid, methylguanidine, and arginine are decomposed at about the same rate as creatinine. It would appear, therefore, that the ring structure of creatinine is but a small factor in determining the specificity of the enzymatic action. On the contrary, the presence of a guanidine-like unit in the molecule appears to be an important determinant of the specificity, since the replacement of one "NH" group by the CO linkage (as in the change from creatinine and creatine to methylhydantoin and methylhydantoic acid) prevents any reaction with the enzyme. It is also interesting that the absence of the methyl group in guanidine (as compared with methylguanidine) markedly reduces the production of urea, as does the shift of the methyl group in creatinine from the 3 to the 5 position.

Cultures of another soil bacillus "HR" have also yielded an enzyme system which attacks creatinine and which is even more specific than the one previously studied. It is shown in Table III that, of the compounds giving the Jaffe reaction which were tested, glycocyamidine is the only one besides creatinine which is attacked by the enzyme, and the rate of its decomposition is far slower than in the case of creatinine; in consideration of the excess of enzyme employed, the inability of the "HR" enzyme to decompose 5-methylglycocyamidine is especially striking.

To determine the effect of the "HR" preparation upon compounds

TABLE IV

ACTION OF "HR" ENZYME ON NON-JAFFE-REACTIVE COMPOUNDS RELATED TO CREATININE 0.200 MG. OF COMPOUND WAS USED IN EACH INSTANCE

(Reprinted from the *Journal of Biological Chemistry*)

COMPOUND	UREA + NH_3 NITROGEN OBTAINED BY HYPOBROMITE METHOD	PERCENTAGE DECOMPOSITION
	mg.	*per cent*
Creatinine	0.0740	100
Creatine	0.0654	100
Glycocyamidine	0	0
Glycocyamine	0	0
Methylhydantoin	0	0
Methylguanidine	0	0
Guanidine acetate	0	0
Arginine	0	0

related to creatinine, but which do not give the Jaffe reaction, advantage was taken of the fact that, when creatinine is acted upon by the enzyme, all the nitrogen is recovered as ammonia plus urea. It is shown in Table IV that the enzyme does not attack glycocyamine, methylguanidine, or arginine, which are decomposed by the "NC" enzyme. Glycocyamidine does not yield any demonstrable amount of urea or ammonia; it will be remembered, however, that this substance is slowly attacked as determined by disappearance of the Jaffe reaction (Table III). It appears, therefore, that the "HR" preparation slowly opens the ring structure of glycocyamidine, but does not decompose the compound further.

With the help of these bacterial enzymes, it has been possible to develop analytical techniques which are highly specific for creatinine and which have been used by several workers for the study of the metabolism of this substance.[6]

Let us mention in passing that it is possible to extract in solution from the cells of one of the creatinine decomposing cultures an enzyme—an anhydrase—which converts creatine into its anhydride creatinine.[7] This reaction offers an opportunity for the study *in vitro* of (a) the enzymatic production of a biologically important cyclic compound from an aliphatic one, and (b) the enzymatic combination of an amino and a carboxyl group to form the CO–NH linkage. Preliminary experi-

ments indicate that, like the creatinine oxidase, the creatine anhydrase exhibits a great specificity with reference to the substrates which it affects.

The decomposition of the capsular polysaccharides of pneumococcus by bacterial enzymes. Virulent pneumococci differ from the avirulent variants of the same bacterial species by the presence of a capsule surrounding the cell. Encapsulated pneumococci can be divided into a number of different serological types, and the type specificity is associated with differences in the chemical composition of the capsular material. The capsular substances of several types of pneumococci have been obtained in a reasonable state of purity and all of them belong to the class of polysaccharides.[8, 9, 10]

On the basis of immunological evidence, it appears therefore that the capsular polysaccharides of the different types of pneumococcus are of paramount importance in determining the serological specificity and conditioning the virulence of these organisms. It was felt that the evidence for this view would become even more convincing if one could obtain specific reagents, enzymes for instance, which, by decomposing the capsular polysaccharides, would render the encapsulated pneumococci inagglutinable in the homologous antisera, and at the same time alter their virulence.

As far as is known, the capsular polysaccharides of pneumococci are not decomposed by enzymes of animal or plant origin, nor are they attacked by common species of bacteria, actinomycetes or molds. It was possible, however, to isolate from soil a new bacterial species, a sporulating bacillus, which hydrolyzes the specific polysaccharide of Type III pneumococcus. A soluble enzyme, capable of catalyzing the same reaction, was separated from cultures of this soil bacillus grown under well defined experimental conditions.[11, 12, 13, 14]

The enzyme depolymerizes the Type III capsular polysaccharide to the aldobionic acid stage. As a result of enzymatic hydrolysis, the capsular substance loses the ability to react *in vitro* with the specific antiserum obtained by immunizing experimental animals with the Type III capsular antigen.

It can be demonstrated by staining reactions that the addition of active enzyme to a suspension of living encapsulated Type III pneumococci causes the disappearance of the capsule; the specific agglutinability of the bacterial cells in the Type III antiserum is at the same time greatly

TABLE V

SPECIFICITY OF THE PROTECTIVE ACTION OF TYPE III ENZYME

(Reprinted from the *Journal of Experimental Medicine*)

INFECTING DOSE OF PNEUMOCOCCUS	ENZYME (LOT 4-α) J.E CC.			NO ENZYME		
				Virulence-controls		
	Pneumococcus Type I	Pneumococcus Type II	Pneumococcus Type III	Type I	Type II	Type III
cc.						
0.1	....	....	S	....	....	....
0.01	....	....	S	....	....	....
0.001	....	....	S	....	....	....
0.0001	D20	D34	S	....	....	....
0.00001	D34	D34	S	D22	D36	D34
0.000001	D34	D34	S	D34	D36	D34
0.0000001	....	....	..	D34	D20	D72

S = survived.
D = Death of animal; the numeral indicates the number of hours before death.
— = not done.

impaired. It is important to mention, however, that the enzyme does not kill the bacterial cells; in fact Type III pneumococci grow readily in media containing the enzyme, but they are deprived of their capsules; when the decapsulated cells are now transferred to a new medium not containing the enzyme, the capsule again reappears and restores to the pneumococci their full virulence and their agglutinability in Type III antiserum. It is clear therefore that the action of the enzyme is directed against the preformed capsular polysaccharide, but does not affect the metabolism of the bacterial cell.

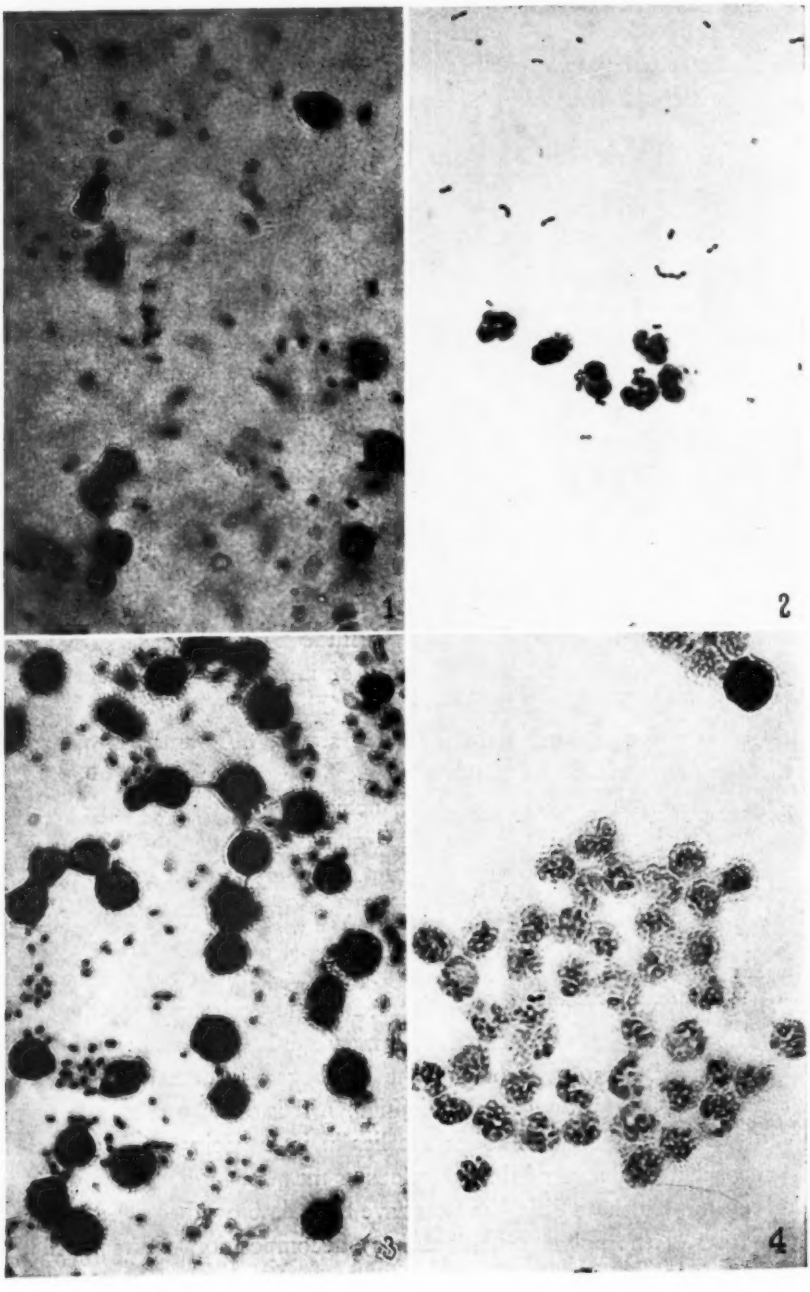
Enzymes capable of attacking the capsular polysaccharides of other pneumococcus types have now been obtained from different strains of soil bacteria.[15, 16, 17, 18, 19] Several of these enzymes exhibit a remarkable specificity, and can differentiate between polysaccharides which give cross reactions in immune antisera; for instance, the polysaccharide of gum acacia which reacts in Type III pneumococcus antiserum is not affected by the enzyme which hydrolyzes the Type III polysaccharide.[13] Even more striking is the difference between the enzymes attacking the polysaccharides of Type III and Type VIII pneumococcus. Both these substances are composed of glucose and glucuronic acid in different ratios, and because of this chemical relationship, they exhibit a certain

amount of cross reaction in immune sera.[20, 21] On the contrary, the bacterial enzymes developed against each one of the polysaccharides fail to attack the other;[19] in other words, the enzymes are even more specific than are the antibodies obtained by immunization of experimental animals.

Not only are the bacterial polysaccharidases capable of hydrolyzing the capsular substances *in vitro*, but they exhibit the same activity *in vivo*. In fact, they can protect experimental animals against infection with virulent pneumococci.[22] In view of the specificity which the enzymes exhibit *in vitro*, it was to be expected that the protection induced would also exhibit a specificity determined by the chemical nature of the capsular polysaccharide of the particular type of pneumococcus used for infection. It is shown in Table V, for instance, that the enzyme which decomposes the Type III capsular substance can protect mice against infection with 1,000,000 fatal doses of pneumococci of this type, but is entirely ineffective against pneumococci of other types. The same polysaccharidase exhibits also a curative effect on the dermal infection of rabbits,[23, 24] as well as on the experimental pneumonia in monkeys of the *M. cynomologos* species, produced with Type III pneumococci.[25]

The mechanism of the protection so induced is revealed by a microscopic study of the peritoneal exudate of mice during the course of infection with Type III pneumococci.[22] The progress of events can be seen in photomicrographs which illustrate the differences in cellular reactions of treated and untreated mice, 2 and 4 hours after injection of one million fatal doses of pneumococci. Two hours after infection, the peritoneal exudate of the untreated mouse (Fig. 1) showed numerous encapsulated cocci free in the fluid. In contrast to this, the pneumococci in the enzyme treated animal at this time (Fig. 2) were devoid of capsules, and only naked bacteria were visible, many of which were already engulfed by leukocytes. At the end of 4 hours, the number of encapsulated pneumococci had increased in the peritoneum of the untreated mouse (Fig. 3); in the treated mouse only an occasional decapsulated organism was seen outside the leukocytes whereas many could be seen within the phagocytic cells (Fig. 4). It is obvious therefore that the protective action of the enzyme lies in its capacity to decompose the capsular substance of the infectious agent.

In summary three different tests have been employed to demonstrate the action of the polysaccharidases: (a) decomposition of the purified


1
2
3
4

capsular polysaccharides, with attendant loss of their specific precipitability in homologous antiserum, (b) destruction of the pneumococcus capsule, both *in vitro* and *in vivo*, (c) protection of experimental animals against infection with virulent pneumococci. All these reactions are type specific. They confirm beyond doubt that the pneumococcus capsules consist of the specific polysaccharides and the latter substances determine the serological specificity of pneumococci and condition their virulence. The polysaccharidases are neither bacteriolytic, nor bactericidal; it is by destroying the protective capsules of the virulent pneumococci that they render the bacteria susceptible to the phagocytic action of the cells of the host, and determine the recovery of the animal.

It is clear that two properties of the enzymes have made possible their application to the study of pneumococcus infections, (a) their specificity, (b) the fact that they can function under physiological conditions. Microbial enzymes have also been used with advantage in studying the chemical nature of bacterial antigens; and there are many other biological problems the analysis of which would be greatly facilitated if enzymes specific for certain substrates were available. The addition of the test substrates to soil or sewage, for instance, will reveal in all cases the existence of microörganisms capable of decomposing them. By isolating these microörganisms in pure culture from the natural

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LEGENDS FOR PHOTOMICROGRAPHS

FIG. 1. Photomicrograph of a stained preparation of the peritoneal exudate of a mouse 2 hours after the intraperitoneal injection of 0.01 cc. of a virulent culture of Type III pneumococcus. The bacteria show well-defined capsules and no evidence of phagocytosis is seen. Many polymorphonuclear and a moderate number of mononuclear leukocytes are present. Gram stain. × 1000.

FIG. 2. Photomicrograph of a corresponding preparation of the exudate of a mouse 2 hours after receiving the same amount of culture together with 0.5 cc. of a preparation of the specific enzyme. The bacteria are devoid of capsules. Polymorphonuclear leukocytes predominate and phagocytosis is evident. Gram stain. × 1000.

FIG. 3. Photomicrograph of a stained film of the peritoneal exudate of a mouse 4 hours after injection with 0.01 cc. of culture alone. The bacteria are increased in number, encapsulated, and extracellular. The cellular elements are polymorphonuclear and mononuclear leukocytes in about equal numbers. Gram stain. × 1000.

FIG. 4. Photomicrograph of a corresponding preparation of the exudate of a mouse 4 hours after receiving the same amount of culture together with 0.5 cc. of a preparation of the specific enzyme. Marked phagocytosis has occurred and only an occasional organism is seen outside the accumulated leukocytes, nearly all of which are of the polymorphonuclear type. Gram stain. × 1000.

[Differences in the density of the backgrounds of these four figures are due to the use of color screens in the photographic reproductions. This technique however, alters none of the essential details observed in the original microscopic preparations. (Reproduced by the courtesy of the *Journal of Experimental Medicine.*)]

sources, and growing them under appropriate conditions, it should often be possible to prepare enzymes adapted for use as specific physiological reagents.

A selective bactericidal principle extracted from cultures of a sporulating bacillus. The preceding discussion has considered the isolation from natural sources of microörganisms capable of decomposing well-defined organic compounds (creatinine, polysaccharides, etc.). It appeared possible that there also exist microörganisms capable of attacking not only soluble, isolated substances, but also the intact living cells of other unrelated microbial species. Specifically, an attempt was made to recover from soil, microörganisms that could attack the living cells of the pathogenic Gram-positive cocci.[26] To achieve this end, suspensions of living pneumococci, streptococci, and staphylococci were added to a soil mixture which was maintained at neutral reaction under aerobic conditions, in the hope that there would develop in the soil preparation a microbial flora antagonistic to the Gram-positive cocci. In fact, it was possible to isolate from the soil preparation an aerobic sporulating bacillus which can multiply at the expense of the living cells of Gram-positive bacteria. Cultures of this soil bacillus have yielded a soluble principle which kills the susceptible bacterial species;[27] the following discussion deals with the nature, properties and activity of this bactericidal principle.

The bactericidal principle of the soil bacillus can be obtained in a protein-free form which is soluble in alcohol and acetone, but insoluble in water and ether.[28] From the alcohol soluble fraction there have been obtained as crystalline compounds three well-defined chemical entities all of which exhibit bactericidal action *in vitro;* they have been called graminic acid, gramidinic acid, and gramicidin with respective molecular weights of 900, 1000, and 1400.[29, 30] Although the complete structure of these substances is as yet unknown, it can be stated at this time that all of them consist largely of amino acids probably combined as polypeptides. Gramicidin which has been most carefully studied contains 2-3 tryptophane residues per molecule; a large percentage of the other amino acids appear to be present in the *d* (so-called unnatural) form; gramicidin also contains an aliphatic fatty acid but contains neither free acid nor basic group. As stated above, the three crystalline substances exhibit a marked bactericidal effect *in vitro*. For instance, 0.005 mg. of gramicidin is sufficient to kill 10^9 pneumococci or virulent streptococci

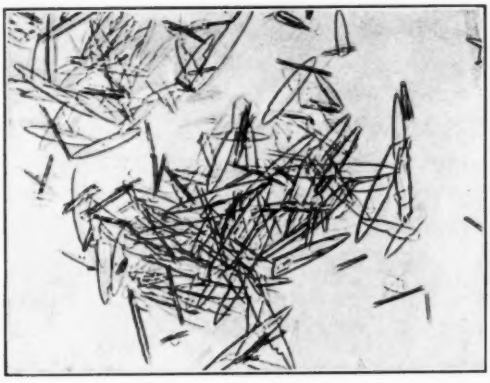

FIG. 5. Photomicrograph of crystals of gramicidin. × 225. (Reproduced by courtesy of Dr. R. D. Hotchkiss.)

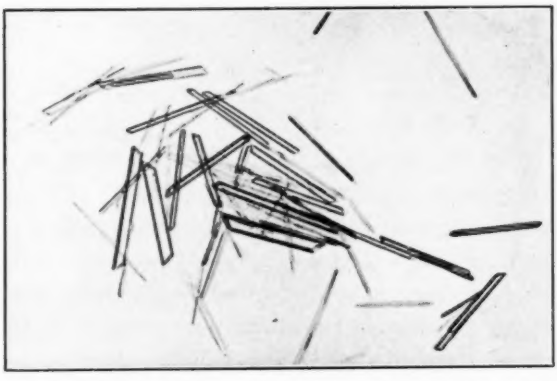

FIG. 6. Photomicrograph of crystals of graminic acid. × 320. (Reproduced by courtesy of Dr. R. D. Hotchkiss.)

within 2 hours at 37° C. Staphylococci, diphtheria bacilli, aerobic sporulating bacilli, in fact all Gram-positive organisms so far tested, are also readily killed under the same conditions although the amount of bacterial substance required varies from one bacterial strain to the other. On the contrary, none of the Gram-negative bacilli have been found to be susceptible, even to much larger amounts of the substance. Meningococci and gonococci are much more susceptible than the Gram-negative bacilli but more resistant than pneumococci or streptococci; this fact may be of some interest, since bacteriologists have often considered the

TABLE VI

PROTECTIVE ACTION OF CRYSTALLINE FRACTION OF BACTERICIDAL AGENT

(All mice infected with 10,000 fatal doses of Type I pneumococcus)

MATERIAL	AMOUNT	NUMBER OF MICE	RESULT		
	mg.				
Graminic acid	0.016	3	D40	D44	D68
"	0.008	3	D40	D40	D48
"	0.004	3	D40	D40	D40
"	0.002	3	D40	D96	D96
"	0	3	D24	D40	D40
Gramicidin	0.010	3	S	S	S
"	0.005	3	S	S	S
"	0.002	3	D61	D114	S
"	0.001	3	D45	D46	S
"	0	3	D27	D27	D32

S = Survival.
D = Death; the numeral indicates number of hours after infection.

Gram-negative cocci as intermediary between the Gram-negative bacilli and the Gram-positive organisms.

In spite of the great activity which they exhibit *in vitro*, both graminic acid and gramidinic acid appear ineffective *in vivo*. On the contrary, one single dose of 0.001 to 0.002 mg. of gramicidin injected into the abdominal cavity, is sufficient to protect mice against 10,000 fatal doses of pneumococci or streptococci (Table VI). Larger amounts of the material, injected on 3 consecutive days will also protect mice against larger infective doses, or cure them of a well-established infection. The bactericidal substance has proven equally effective against infection with the 5 different types of pneumococci and the 14 different types of hemolytic streptococci (groups A and C) which have been tested; it is permissible to hope, therefore, that it will also prove effective against all virulent strains of these bacterial species irrespective of type specificity; in fact preliminary experiments have recently demonstrated that it does also protect mice against certain strains of staphylococci. On the contrary as could be expected from the *in vitro* experiments, no protection could be obtained against infection of mice with *Klebsiella pneumoniae* (Type B), a Gram-negative bacillus.

Gramicidin is very insoluble in aqueous media; this insolubility may account for the fact that the substance is ineffective against pneumococcus peritonitis in mice when administered by any route (intravenous, intramuscular, subcutaneous) other than the intra-abdominal. Very recently, it has been possible to obtain from autolyzed cultures of the sporulating soil bacillus, a form of the bactericidal substance which is readily soluble in water at neutral reaction; not only does the new preparation cure mice of pneumococcus and streptococcus peritonitis when administered intra-abdominally, but it is also effective by the subcutaneous and intravenous route. Although much remains to be learned about this soluble fraction, it is evident that in some respects it is more effective *in vivo* than the crystalline substance which has been described under the name of gramicidin.

The findings just reported have revealed the existence and to some extent the chemical nature of a new type of bactericidal agent, which, although extremely active against many different species of Gram-positive microörganisms, fails to attack the Gram-negative bacilli. It can be said, therefore, that this new bactericidal principle exhibits a specificity of a peculiar order, one which is correlated with the staining characteristics of the bacterial cells. Since the staining properties are necessarily conditioned by chemical and physical characters of cellular structure, it is perhaps permissible to state that the specificity of the bactericidal agent is related to some structural difference between the Gram-positive and the Gram-negative cells. An analysis of the mechanism of the bactericidal action[31] may therefore reveal important facts concerning cellular structure; this knowledge in turn may indicate what type of chemical structure can be expected to exhibit affinity for the cellular structure of the different bacterial species and may suggest new avenues of approach to the problem of antisepsis. It is also of obvious importance to establish the chemical differences between graminic acid and gramicidin which determine that only the latter is active *in vivo*, whereas both are equally active *in vitro*. This knowledge will give us a clue as to the factors which allow an antiseptic to remain active in the presence of animal tissues, and which thus render it a therapeutic agent.

Finally it is permissible to hope that one will also discover in nature microörganisms antagonistic to other types of pathogens and that the active substances by means of which they exert their antagonistic effect will be isolated. These agents may not themselves be effective in the

animal body. An understanding of their chemical structure and of the mechanism of their action should, however, give the bacteriologist and the chemist useful information and new compounds for the development of chemotherapy on a rational basis.

The adaptive production of enzymes by bacteria. It is apparent that the biologist will discover in the microbial world a great variety of useful reagents. On the other hand it is also true that microbial life has revealed a number of physiological processes of general biological significance. For instance, cultural conditions greatly affect the enzymatic constitution of the microbial cell. In some cases in particular, the production of a given enzyme is stimulated when the substrate which it attacks is a component of the culture medium. The bacillus which hydrolyzes the capsular polysaccharide of Type III pneumococcus does not form the specific enzyme when cultivated in ordinary peptone media (in which growth is very abundant), whereas the polysaccharidase is readily produced when the same organism is compelled to use the specific polysaccharide in the course of its growth.[11, 12, 13] Similarly, the "NC" culture which attacks creatinine grows abundantly in peptone solutions, but forms the creatinine oxidase only when creatine or creatinine is a constituent of the culture medium.[5, 7] Karström designated as "adaptive" those enzymes which are produced as a specific response to the presence of the homologous substrate in the culture medium; he differentiated them from the "constitutive" enzymes which are always formed by the cells of a given species, irrespective of the cultural conditions.[33]

Adaptive enzymes exhibit a great specificity with reference to the substrates which they attack, a property which suggests their use in the analysis of biological problems; it is of practical importance therefore, to develop satisfactory techniques for their production. One may wonder also whether the readiness with which microörganisms selectively change their enzymatic constitution in response to changes in the environment may not be of importance in determining the pathology of infectious diseases. Is it not possible that a pathogenic agent growing in living animal tissues may differ in important respects from the same agent grown in laboratory media? In other words, the pathogenic agent may produce during the infectious process, a number of substances which do not appear during growth in the standard laboratory media, and which are the result of the reaction between the para-

site and the tissues of the infected host. These products might account for some of the obscure reactions of infection.

In any case, the very mechanism of production of adaptive enzyme by microörganisms challenges the bacterial physiologist; nothing is known of this mechanism.[32, 33, 34, 35] It seems established that the change in enzymatic construction which results in "adaptation" does not necessarily require the production of new cells. Although production of adaptive enzymes has been described to occur in the absence of cellular division, all evidence available indicates that this formation always involves the synthesis of new protoplasm. It is possible that the synthetic process is, so to speak, oriented or guided by the chemical structure of the substrate, which thus determines the specificity of the enzyme evoked. And it is a common fact, as already pointed out, that adaptive enzymes exhibit a remarkable specificity toward the substrates which stimulate their production.

The phenomenon of adaptive production of enzymes offers great practical possibilities to the bacteriologist. Even more important perhaps, it brings him back into the main channels of biological thought, to the biological problem "par excellence," the problem of adaptation. The study of the mechanism whereby microörganisms produce those enzymes which appear as an adaptive response to the presence of the homologous substrates in the culture medium, bids fair to throw light on some of the reactions involved in specific adaptation.

REFERENCES

1. Pasteur, L. Mémoire sur la fermentation appelée lactique, *Mém. de la Soc. d. sc., de l'agric. et d. arts de Lille,* 1857 (Aug. 3).
2. Pasteur, L. Mémoire sur la fermentation alcoholique, *Compt. rend. Acad. d. sc.,* 1857, *45:* 1032.
3. Pasteur, L. Mémoire sur la fermentation de l'acide tartrique, *Compt. rend. Acad. d. sc.,* 1858, *46:* 615.
4. Pasteur, L. Note relative au *Pencillium glaucum* et à la dissymmétrie des produits organiques naturels, *Compt. rend. Acad. d. sc.,* 1860, *51:* 298.
5. Dubos, R. J. and Miller, B. F. Production of bacterial enzymes capable of decomposing creatinine, *J. Biol. Chem.,* 1937, *121:* 429.
6. Miller, B. F. and Dubos, R. J. Studies on presence of creatinine in human blood, *J. Biol. Chem.,* 1937, *121:* 447.
7. Dubos, R. J. and Miller, B. F. Bacterial enzyme which converts creatine into its anhydride creatinine, *Proc. Soc. Exper. Biol. & Med.,* 1938, *39:* 65.
8. Avery, O. T. Role of specific carbohydrate in pneumococcus infection and immunity, *Ann. Int. Med.,* 1932-33, *6:* 1.
9. Avery, O. T. Chemo-immunologische Untersuchungen an Pneumokokken-Infektion und Immunität, *Naturwiss,* 1933, *21:* 777.
10. Heidelberger, M. The chemical nature of immune substances, *Physiol. Rev.,* 1927, *7:* 107.
11. Dubos, R. J. Factors affecting yield of specific enzyme in cultures of bacillus decomposing capsular polysaccharide of

type III pneumococcus, *J. Exper. Med.*, 1932, *55:* 377.

12. Dubos, R. J. Studies on the mechanism of production of specific bacterial enzyme which decomposes capsular polysaccharide of type III pneumococcus, *J. Exper. Med.*, 1935, *62:* 259.
13. Dubos, R. J. and Avery, O. T. Decomposition of capsular polysaccharide of pneumococcus type III by bacterial enzyme, *J. Exper. Med.*, 1931, *54:* 51.
14. Dubos, R. J. and Bauer, J. H. Use of graded collodion membranes for concentration of bacterial enzyme capable of decomposing capsular polysaccharide of type III pneumococcus, *J. Exper. Med.*, 1935, *62:* 271.
15. Shaw, M. Decomposition of pneumococcus carbohydrate by the combined activity of strains of two bacterial species, *J. Bacter.*, 1937, *33:* 644.
16. Sickles, G. M. and Shaw, M. Microorganisms which decompose the specific carbohydrate of pneumococcus types II and III, *J. Infect. Dis.*, 1933, *53:* 38.
17. Sickles, G. M. and Shaw, M. Action of microorganisms from soil on type-specific and nontype-specific pneumococcus type I carbohydrates, *Proc. Soc. Exper. Biol. & Med.*, 1933-34, *31:* 443.
18. Sickles, G. M. and Shaw, M. Systematic study of microörganisms which decompose specific carbohydrates of pneumococcus, *J. Bact.*, 1934, *28:* 415.
19. Sickles, G. M. and Shaw, M. Microörganism which decomposes specific carbohydrate of pneumococcus type VIII, *Proc. Soc. Exper. Biol. & Med.*, 1934-35, *32:* 857.
20. Goebel, W. F. Chemo-immunological studies on soluble specific substance of pneumococcus, *J. Biol. Chem.*, 1935, *110:* 391.
21. Heidelberger, M., Kabat, E. A. and Shrivastava, D. L. Quantitative study of cross reaction of type II and type III pneumococci in horse and rabbit antisera, *J. Exper. Med.*, 1937, *65:* 487.
22. Avery, O. T. and Dubos, R. J. Protective action of specific enzyme against type III pneumococcus, *J. Exper. Med.*, 1931, *54:* 73.
23. Goodner, K., Dubos, R. J. and Avery, O. T. Action of specific enzyme upon dermal infection of rabbits with type III pneumococcus, *J. Exper. Med.*, 1932, *55:* 393.
24. Goodner, K. and Dubos, R. J. Studies on quantitative action of specific enzyme in type III pneumococcus dermal infections in rabbits, *J. Exper. Med.*, 1932, *56:* 521.
25. Francis, T., Jr., Terrell, E. E., Dubos, R. J. and Avery, O. T. Experimental type III pneumococcus pneumonia in monkeys; treatment with enzyme which decomposes specific capsular polysaccharide of pneumococcus type III, *J. Exper. Med.*, 1934, *59:* 641.
26. Dubos, R. J. Studies on bactericidal agent extracted from soil bacillus; preparation of agent, *J. Exper. Med.*, 1939, *70:* 1.
27. Dubos, R. J. Studies on bactericidal agent extracted from soil bacillus; protective effect of bactericidal agent against experimental pneumococcus infections, *J. Exper. Med.*, 1939, *70:* 11.
28. Dubos, R. J. and Cattaneo, C. Studies on bactericidal agent extracted from soil bacillus; preparation and activity of protein-free fraction, *J. Exper. Med.*, 1939, *70:* 249.
29. Hotchkiss, R. D. and Dubos, R. J. Fractionation of the bactericidal agent from cultures of a soil bacillus, *J. Biol. Chem.*, 1940, *132:* 791.
30. Hotchkiss, R. D. and Dubos, R. J. Chemical properties of bactericidal substances isolated from cultures of a soil bacillus, *J. Biol. Chem.*, 1940, *132:* 793.
31. Dubos, R. J. A selective bactericidal agent extracted from the cells of a sporulating bacillus, *Proc. Third Internat. Cong. Microbiol.*, 1939: 261.
32. Dubos, R. J. Enzymatic analysis of the antigenic structure of pneumococci, *Ergebn. d. Enzymforsch.*, 1939, *8:* 135.
33. Karström, H. Enzymatische Adaptation bei Mikroorganismen, *Ergebn. d. Enzymforsch.*, 1938, *7:* 350.
34. Dubos, R. J. The adaptive production of enzymes in bacteria, *Bact. Rev.*, 1940, *4:* 1.
35. Yudkin, J. Enzyme variation in microorganisms, *Biol. Rev.*, 1938, *13:* 93.

THE PRESENT STATUS OF THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*

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In presenting an analysis of methods of treatment of subacute bacterial endocarditis, it is well at the outset to say a few words about the criteria for diagnosis. Only reports of those patients having positive blood cultures of Streptococcus viridans will be included in this discussion. It is, of course, generally known that in many patients it is not possible to recover the organisms from the blood, yet at autopsy the characteristic pathological changes are found on the heart valves and organisms can be recovered from the valves. For the purposes of analysis, however, such cases will have to be excluded from our discussion. Organisms other than strains of Streptococcus viridans, namely staphylococci, Streptococcus hemolyticus and gonococci, have been described as causing subacute bacterial endocarditis. One could easily see how difficult it would be if the field were broadened to include these organisms.

It will also be necessary to include only those cases having well-established clinical evidence of endocarditis because, as Hamman[1] pointed out in 1937, it is possible for the streptococcus "to invade the blood stream when there is infection in the upper respiratory tract and no doubt less frequently with infections located elsewhere. Therefore, the presence of bacteria in the blood during the course of a febrile reaction does not signify that the endocardium has become infected, unless at the same time there is undisputed evidence of a valvular lesion or a congenital defect and other characteristic symptoms of bacterial endocarditis are present." Another important bit of confusion which enters into the discussion of treatment is the difficulty many times in differentiating between a recurrence of rheumatic activity and subacute bacterial endocarditis. This difficulty extends even to the blood culture. In 1929 Cecil, Nicholls and Stainsby[2] recovered Streptococcus viridans

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strains from the blood of rheumatic patients in a high percentage of cases. In 1933 Callow[3] reported an incidence of 70 per cent positive blood cultures in rheumatic active patients, and of these 35 per cent showed Streptococcus viridans. It should be stated, however, that Cecil, Nicholls and Stainsby and Callow did not obtain the organisms from the blood stream of patients with rheumatic fever with as great ease as is usually possible in a fresh case of subacute bacterial endocarditis. It is evident, then, that some cases of supposed subacute bacterial endocarditis superimposed on old rheumatic valves are in fact cases of recurrent rheumatic activity and any treatment which has apparently caused the infection to subside merely coincided with the natural and spontaneous remission of the rheumatic infection. This is especially true if organisms are recovered with difficulty from the blood stream or if special techniques are used. It is obvious, also, that the disease must be well along its course because early diagnosis is difficult and often impossible. Treatment, therefore, given to the so-called early cases, although desirable, cannot be decisive because the diagnosis is frequently open to question.

Subacute bacterial endocarditis is a disease in which spontaneous remissions are said to occur. It has not been my privilege, however, to have ever witnessed such a case. Every patient with this disease that I have seen on the Third Medical Division at Bellevue Hospital and in my private practice since 1921 has finally succumbed. Hamman[1] as late as 1937, said this of Johns Hopkins Hospital: "As far as I know the uniform mortality of the disease at that hospital has not changed during the last 12 years. Certain I am, that no well-established instance of subacute bacterial endocarditis, which has been under my observation has ever recovered." If we exclude the so-called epidemic reported by Oille, Graham and Detweiler,[4] the largest number of spontaneous remissions is reported by Libman.[5, 6] From his vast experience with this disease Libman gives the incidence of spontaneous recovery as about 3 per cent. He is certain of at least twenty-five cases, and there are probably others among those where a proper follow-up could not be carried on. Capps[7] is of the opinion that virulence varies from year to year and that since 1924 we have had a much more virulent form of the disease than prior to that date. This is not concurred in by Libman. Granting, then, that spontaneous remissions are possible, this fact must of necessity be considered in the evaluation of any form of treatment.

Many patients reported as benefiting by some forms of treatment,

have eventually died and at autopsy evidence of healing in diseased valves is noted. This is sometimes considered as indicating some beneficial effect of the treatment. However, in the natural course of the disease we find that the attachment of the vegetation is the seat of an organizing reaction like that of healing. In order to be certain that the treatment affected the course of the disease bacteria must be found in the valves themselves. This, taken in conjunction with the healing reaction is evidence of the effectiveness of the treatment. Very few observers have followed this rigid method of control.

Because of the anatomical peculiarities of the characteristic valvular lesion the difficulties in treatment are considerably increased. As Friedman[8] has pointed out, "The entire process is surrounded by dense fibrin and platelets, deposited by the blood stream, which isolates the proliferating bacteria from the possibility of contact with any agent not dissolved in the blood plasma. Because of these facts, it would be best to consider subacute bacterial endocarditis as an infection characterized by masses of bacteria growing in fibrin, suspended in and yet isolated from the blood stream."

As summarized by Andrews three main difficulties, then, exist in the evaluation of forms of treatment:

1. "The difficulty that exists in certain cases in establishing the diagnosis."
2. "The possibility of spontaneous recovery."
3. "The anatomical peculiarities of the site of the infection and of the lesion, which render the organisms difficult to reach by therapeutic agents."

Treatment Other Than With Sulfonamide Derivatives

Probably no disease has had as many remedies. This fact alone speaks for the futility of most of them. Non-specific supportive treatment will always be of value. These measures include blood transfusions for anemia, supplemental vitamins and minerals in the diet or otherwise, and drugs or physical measures for treatment of symptoms as they arise. In any treatment directed toward the etiological agent this part of the therapy will always be important.

In 1936 Riesman, Kolmer and Polowe[9] advocated removal of the spleen as a therapeutic procedure. Because in this disease the spleen is often the site of multiple infarctions, they reasoned that the spleen was

a sort of "branch factory," acting as a secondary focus in the multiplication of bacteria. In their opinion, therefore, its removal would make it easier for the normal processes of recovery to take place. Their results are not particularly encouraging; of the four patients operated on, three died, and in the fourth who survived, "No definite diagnosis was arrived at—mural subacute bacterial endocarditis seemed reasonable."[9] In 1939 Polowe[10] reported one case of apparent cure. In reviewing the protocol of this case I am not convinced that, if our criteria are kept with proper rigidity, this case can be classified as true subacute bacterial endocarditis. It is probable that, with chemotherapy offering the hope it does, splenectomy will fall into the discard.

Even before the days of sulfonamide derivatives many chemical substances have been used as specific agents, arsenic compounds in particular. Capps[7] reported four cures with sodium cacodylate. He expresses considerable surprise and also admits that after these four cases he has never been able to get the same satisfactory results. Arsenical compounds are known to exert a powerful stimulus on the reticulo-endothelial system, resulting in increased phagocytosis and in the production of immune substances. In this connection the experience of Lippman[11] is interesting. He gave a patient with subacute bacterial endocarditis sulfanilamide, neoprontosil and sulfapyridine with only slight improvement. On giving ammonium hepten-chlorarsonate, the temperature became normal; there were no further emboli, and the patient had been up and about for three and one-half months at the last observation. In contrast to this is the fact that seven patients in a series of 250 patients soon to be reported by Kelson[12] were given arsenicals with no apparent benefit.

The Sulfonamide Derivatives

Naturally the first drug to be used of the series was sulfanilamide. Long[13] has five recoveries out of 120 patients treated. "All of these patients are in as good health as their underlying cardiac condition will permit them to be, and they have gone on an average of two and a half years without any recurrence of their infection." Heyman[14] reports a remission of 18 months in a patient whose underlying heart disease is patent ductus arteriosus. In general, however, results with this drug are not encouraging. Solway and Pritzker[15] report a death in spite of intensive treatment. Spink and Crago[16] report twelve cases with two apparent recoveries. However, one of these patients was infected with Staphylococ-

cus aureus, so we can actually count one cure in their series. They conclude that the treatment is of doubtful value. Major[17] used other members of the sulfonamide group as well as sulfanilamide and reports two apparent cures after the disease had been quiescent one year, and nine months respectively. The first patient received neoprontosil and prontosil and then sulfapyridine. The second patient received sulfapyridine alone. One other patient with advanced heart disease died of congestive heart failure and autopsy showed healed mitral and aortic valves. This patient had received prontosil and sulfanilamide. The eventually fatal termination in three other patients was in no way influenced by sulfapyridine and prontosil. Andrews[18] reports a recovery following intensive therapy with sulfapyridine. However, his patient had one negative blood culture. No others were taken. In April 1940 Kinell and Ernstene[19] from the Cleveland Clinic reported five patients with subacute bacterial endocarditis treated unsuccessfully with sulfapyridine. Two of these cases were identified with Streptococcus viridans, two with non-hemolytic streptococci, and the other with an anaerobic streptococcus. Kelson and White's[20] experience with the sulfonamide derivatives alone was disappointing. In forty-six patients receiving sulfanilamide an occasional reduction of fever and sterilization of the blood stream resulted, but there was no lasting benefit in any instance. They gave sulfapyridine alone to ninety-seven patients and found that in the majority the temperature was lowered, with frequent sterilization of the blood stream. Except in a single instance, however, these effects were temporary; "escape" occurred in from a few days to two months. The one patient apparently cured was not infected with Streptococcus viridans but with the gonococcus, together with a non-hemolytic anaerobic streptococcus. In nineteen cases, sulfathiazole was given and only temporary improvement was noted in four cases.

It might be well at this point to consider briefly the chemotherapeutic problem presented by this disease. In 1938 Friedman[8] made a study of the fibrin factor in its relation to subacute bacterial endocarditis. At the same time he described the properties any chemotherapeutic agent must have to be effective in this disease. They are well worth quoting here:

1. "It or its *in vivo* breakdown products must not be neutralized by the proteins of the blood stream to such an extent that the bactericidal properties are nullified.

2. "It must be able to permeate the fibrin mass which surrounds the organism.
3. "It must be able to remain in the blood stream long enough and in sufficiently high concentration so that it can permeate the fibrin in a quantity sufficient for bactericidal purposes and at the same time not affect the host adversely."

The sulfonamide derivatives generally used satisfy the first criterion but fail in the other two. The inability of sulfanilamide, sulfapyridine and sulfathiazole to penetrate blood clots *in vitro*, as shown by Duncan and Faulkner,[21] is in accord with the clinical observation of their inability or difficulty in penetrating the fibrin network on the valves in subacute bacterial endocarditis. These observers, however, believe that even with this handicap, eradication of the infection is possible because "In the course of time all of the preëxisting thrombi should become organized into fibrous scar tissue while all newly formed thrombi in a patient under active treatment will be impregnated with the drug. Thus, conditions will tend to become less and less favorable for growth of the organism if an effective drug is taken continuously over a long period of time." Whether or not this theory is correct could not be tested from the published case reports. Insufficient data on methods of dosage and amounts as well as an inadequate number of observations on blood level of the drug, if these observations were made at all, made it impossible to analyze the results of treatment.

An ingenious method of getting around this problem of the fibrin clot is the technique developed and reported simultaneously by Kelson and White,[20] and by Friedman, Hamburger and Katz.[22] The latter authors report one case with an unfavorable result, whereas Kelson and White report favorable results in two of six patients with subacute bacterial endocarditis. The method now used by Kelson and White is as follows:

Sulfapyridine is given in large doses to bring the blood level above 5 mgm. per 100 cc. for 4 to 7 days. Heparin is then given by uninterrupted intravenous drip day and night for 14 days. The solution of heparin was originally made as follows: the contents of a 10 cc. vial of heparin (10,000 units) was added to 500 cc. of physiological saline. However, because of the high salt intake with this method, edema developed; therefore, the present technique is to use distilled water with 5 per cent of glucose and heparin. Occasionally, in patients already

edematous, 10 per cent glucose, which is mildly dehydrating, is used instead. Kelson and White now have a total of twenty-seven patients treated with this method. Three patients are well and physically active several months after completing therapy, one patient was well and active for a time but had a recrudescence of his disease following a tooth extraction, and another patient died in congestive heart failure. At autopsy this patient showed complete healing of the bacterial lesion with complete absence of bacteria in the lesion.

The use of heparin is based on the *in vitro* experiments that heparin will arrest the deposition of platelets and fibrin. Granting that this also takes place *in vivo* on the heart valves, such action prevents organisms from becoming enmeshed in fibrin to such an extent that they cannot be reached by the sulfonamide derivatives.

Kelson and White[20] do not believe that this method causes a tendency to spontaneous hemorrhage, particularly cerebral hemorrhage. Although they had two cerebral deaths in their twenty-seven patients, they are of the opinion that the incidence of hemorrhage is no greater than occurs spontaneously in the natural course of the disease. In explaining the high percentage of unsatisfactory results they point out that the previous use of sulfonamide derivatives, particularly sulfapyridine, may render the organisms fast to the drug and thus prevent complete sterilization of the blood stream and heart valves. As far as I know, Kelson and White are the only authors reporting favorable results with this method. Friedman, Hamburger and Katz[22] and more recently Kleiber[23] report fatalities. Long[13] states that he has not been impressed by heparin and considers it a dangerous adjunct to treatment.

Another method of approach is the combination of intensive treatment with a sulfonamide derivative plus the raising of the body temperature either by typhoid-paratyphoid vaccine as advocated by Solomon,[24] or the use of hyperthermia by physical means as described by Bierman and Baehr.[25] The experimental basis for this work was furnished by H. J. White and Parker.[26] They demonstrated that the effectiveness of sulfonamide derivatives increased considerably with a rise in temperature. Solomon's technique is to give sulfapyridine in large doses until a high blood level for the drug is reached, and then to give typhoid-paratyphoid injections intravenously nightly for seven nights. Solomon was kind enough to give me his final figures; of seventeen patients who received treatment, five have apparently recovered.

In reviewing the protocols, however, we find only three of these had Streptococcus viridans in the blood stream, one other case had non-hemolytic streptococcus and in the other there was merely the statement that the blood culture was positive. All five recoveries took place in the first eight cases studied; there were no recoveries in the last nine cases. It may be said in all fairness, however, that only four of these nine were considered by Solomon to have been adequately treated. Bierman and Baehr[25] report the use of the combination of chemotherapy, either sulfanilamide or sulfapyridine with physically induced elevation of the body temperature. Out of sixteen patients, each of whom received six or more bouts of temperature elevation in conjunction with medication, but two made recoveries, and only one of these was due to Streptococcus viridans; in the other patient B. influenzae was isolated from the blood stream. In still another case a patient has made an apparent recovery for 2 months, but the authors consider this as too short a time to make a positive statement as to recovery. There is some danger connected with the technique, namely a rapid heart rate, hyperexia, rapid respiration. In contrast to the reports of Solomon[24] and of Bierman and Baehr[25] we have the report by Krusen and Bennett[27] of six patients unsuccessfully treated with sulfanilamide and hyperthermia.

Such is the present status of the treatment of subacute bacterial endocarditis. No form of therapy which at present seems to offer some hope of cure in a small proportion of the cases has received the really crucial test of new therapeutic procedures, namely confirmation of the results by other investigators. At best all we expect at the very outside from these newer forms of treatment is that an occasional patient may survive, whereas, before, there was an almost uniformly fatal ending. One must consider, also, the occurrence of spontaneous remissions and even cures at certain times in the evaluation of any form of treatment. It is indeed curious that all observers reporting cases seem to have the greatest number of recoveries in the first few cases. Solomon had five recoveries in the first eight cases; none in the next nine. Long had five recoveries in the first fifty cases and none in the next seventy. Kelson and White had two recoveries in the first six cases and only one more recovery in the next twenty-one cases. Is this merely a peculiar coincidence, or might it be related to the fact that subacute bacterial endocarditis may be due to a number of different strains of Streptococcus viridans, strains whose virulence varies greatly? May not certain strains

respond easily to specific forms of therapy or even permit spontaneous recovery? Most observers have neglected to identify the particular strain of Streptococcus viridans in each case, so that for the present these questions must remain unanswered. However, there is experimental evidence to show that the identification of the particular strain is important in regard to virulence.

Fox[28] studied the relationship of strains of green streptococci to the clinical character of subacute bacterial endocarditis and on the basis of his work was able to make the following classification:

Group 1 was characterized clinically by a rapid, stormy course with death in a few months. The strains isolated were salivarius and equinus corresponding to Lancefield's human group.

Group 2 was characterized clinically by a slow course ending with an episode that led to death. The strain isolated was a human form of a rough and G type of Streptococcus non-hemolyticus.

Group 3 was characterized by a slowly progressive course with marked anemia and cachexia so that the patient died without any flagrant episodes. Two types of organisms were found: Streptococcus ignavus, the human smooth form, and Streptococcus non-hemolyticus number 1, a rough non-human form.

Group 4 is the most interesting group because here we have the recurrent cases and possibly those that may be cured. Most of the cases in this group were due to Streptococcus fecalis and one to Streptococcus salivarius.

In general one may say that the slower the course the more apt is the organism to be of the non-human type.

In May of this year Swain[29] described the results of treatment of four patients with sulfonamide compounds and correlated the results with the strains of streptococci. In simple *in vitro* tests he found that the two strains isolated from cases clinically influenced by treatment were susceptible to the drug, whereas the strains isolated from the two cases which resisted treatment were also resistant to the drugs *in vitro*. He suggests that the existence of resistant strains of Streptococcus viridans may be responsible for the failure of some cases to respond to sulfonamide therapy. It would seem highly important, then, in a therapeutic study to make certain of the strain of Streptococcus viridans one is dealing with, and also to study *in vitro* the effect of drugs on the particular organism isolated to determine possible drug resistance of that

particular strain.

It is quite possible that we may find one form of treatment effective for one strain, another for a different one. The drug itself is also important. It is known that slight modification of chemical structure may modify profoundly the ability of the drug to cross cell membranes. This factor would undoubtedly affect the penetrability of tissues as well. Further modification of the sulfonamide compounds or a new compound altogether may give us a drug of greater penetrability than those at present available.

Although this review indicates that no form of treatment for subacute bacterial endocarditis so far devised is very encouraging, yet there are definite indications that the therapeutic problems presented by this disease are now being attacked in a scientific manner. It would appear that we have every reason to believe that further advances will shortly be made and we can look forward to more recoveries than are seen at present.

Addendum

Since this report was read, and just before publication, an article by S. S. Lichtman and William Bierman entitled "Subacute Bacterial Endocarditis: Present Status" appeared in the *Journal of the American Medical Association*, 1941.[30] This article emphasizes the treatment as advocated by Bierman and Baehr and tabulates other forms of treatment.

REFERENCES

1. Hamman, L. Healed bacterial endocarditis, *Ann. Int. Med.*, 1937-38, *11:* 175.
2. Cecil, R. L., Nicholls, E. E. and Stainsby, W. J. Bacteriology of blood and joints in rheumatic fever, *J. Exper. Med.*, 1929, *50:*617.
3. Callow, B. R. Bacteriological investigation of the blood in rheumatic fever, *J. Infect. Dis.*, 1933, *52:*279.
4. Oille, J. A., Graham, D. and Detweiler, H. K. A further report on a series of recovered cases of subacute bacterial endocarditis, *Tr. A. Am. Physicians*, 1924, *39:*227.
5. Libman, E. Further report on recovery and recurrence in subacute bacterial endocarditis, *Tr. A. Am. Physicians*, 1933, *48:*44.
6. Libman, E. *Personal communication.*
7. Capps, J. A. Subacute bacterial endocarditis due to Streptococcus viridans with special reference to prognosis, *Ann. Int. Med.*, 1939-40, *13:*280.
8. Friedman, M. A study of the fibrin factor in its relation to subacute endocarditis, *J. Pharmacol. & Exper. Therap.* 1938, *63:*173.
9. Riesman, D., Kolmer, J. A. and Polowe, D. Splenectomy in the treatment of subacute bacterial endocarditis, *Am. J. M. Sc.*, 1936, *192:*475.
10. Polowe, D. Splenectomy in the treatment of proved subacute bacterial endocarditis; report of a case and review of the literature, *Arch. Surg.*, 1939, *38:* 139.
11. Lippmann, K. Subacute bacterial endo-

carditis—new method of treatment, *New York State J. Med.*, 1940, *40*:524.

12. Kelson, S. R. *Personal communication.*
13. Long, P. *Personal communication.*
14. Heyman, J. Subacute bacterial endocarditis successfully treated with sulfanilamide, *J. A. M. A.*, 1940, *114*:2373.
15. Solway, L. J. and Pritzker, H. G. Sulfanilamide in the treatment of bacterial endocarditis, *Canad. M. A. J.*, 1939, *40*: 543.
16. Spink, W. W. and Crago, F. H. Evaluation of sulfanilamide in the treatment of patients with subacute bacterial endocarditis, *Arch. Int. Med.*, 1939, *64*: 228.
17. Major, R. H. The effect of sulfanilamide compounds on endocarditis, *Am. J. M. Sc.*, 1940, *199*:759.
18. Andrews, C. T. Bacterial endocarditis: possibility of cure by sulphonamides, with report of a case, *Brit. M. J.*, 1940, *1*:5.
19. Kinell, J. and Ernstene, A. C. Subacute bacterial endocarditis treated unsuccessfully with sulfapyridine, a report of five cases, *Cleveland Clin. Quart.*, 1940, *7*:83.
20. Kelson, S. R. and White, P. D. A new method of treatment of subacute bacterial endocarditis, *J. A. M. A.*, 1939, *113*: 1700.
21. Duncan, C. N. and Faulkner, J. M. Penetration of blood clot by sulfanilamide, sulfapyridine, sulfathiazole and sulfamethylthiazole, *Am. J. M. Sc.*, 1940, *200*:492.
22. Friedman, M., Hamburger, W. W. and Katz, L. N. Use of heparin in subacute bacterial endocarditis, *J. A. M. A.*, 1939, *113*:1702.
23. Kleiber, E. E. Subacute bacterial endocarditis treated unsuccessfully with sulfapyridine and heparin, *J. A. M. A.*, 1940, *115*:1713.
24. Solomon, H. A. *Personal communication.*
25. Bierman, W. and Baehr, G. Pyrexia and chemotherapy in bacterial endocarditis, *J. A. M. A.*, 1941, *116*:292.
26. White, H. J. and Parker, J. M. Bactericidal effect of sulfanilamide upon beta hemolytic streptococci in vitro, *J. Bact.*, 1938, *36*:481.
27. Krusen, F. H. and Bennett, R. L. Unsuccessful treatment of subacute bacterial endocarditis with combined fever and sulfanilamide therapy, *Proc. Staff Meet., Mayo Clin.*, 1940, *15*:328.
28. Fox, H. The relationship of strains of green streptococci to the clinical character of subacute bacterial endocarditis, *J. Infect. Dis.*, 1936, *58*:230.
29. Swain, R. H. A. Strain variations in the resistance of Streptococcus viridans to sulphonamide compounds, *Brit. M. J.*, 1940, *1*:722.
30. Lichtman, S. S. and Bierman, W. Subacute bacterial endocarditis; present status, *J. A. M. A.*, 1941, *116*:286.

TREATMENT OF INFECTIONS BY METHODS OTHER THAN CHEMOTHERAPY*

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THIS review confines itself almost entirely to the use of specific therapeutic serums, referring only when necessary to the synergistic action of antiserums and some of the newer chemotherapeutic agents, and to therapy with bacteriophage. The therapeutic efficacy of bacteriophage and the present status of serums in such diseases as scarlet fever, measles, chicken pox, diphtheria, tetanus, staphylococcal and gas bacillus infections, anthrax and botulism will be discussed. The prophylaxis of tetanus is included because the greater number of investigators have concentrated on the production of active immunity against this infection rather than passive immunity or treatment.

In a general review of this nature, it may be well to state at first some rules which are generally applicable to the therapeutic use of serums in all infections. Most of these are well known; nevertheless, some are not followed, and the importance of others is overlooked.

Therapeutic results are so much better when a sufficient dosage of serum is administered early in the disease that delay must be avoided. It is also important that a large enough dose should be injected initially, as in many instances, if this is done, optimum results will be obtained, and no further injections will be necessary. In some infections, however, the nature of the disease is such that repeated injections of serum are required.

In patients who are critically ill with severe infections, there is no question but that the intravenous route is the method of choice, and might be the only way in which some lives may be saved. The advantage of this is that the therapeutic serum is delivered immediately throughout the entire body, and valuable time is not lost as is the case with serum administered by other routes, when there is considerable delay before absorption into the blood stream occurs.

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It is not generally realized that it takes from 16 to 18 hours after serum has been injected intramuscularly for the maximum titer of its antibodies to occur in the blood stream, whereas this occurs immediately with intravenous injection. When identical doses are injected by both routes, the titer eventually reached is only half as high after intramuscular as after intravenous injection.

Undoubtedly, intravenous injections are not used more often because there is a definite element of risk of anaphylactic shock or death when even the most carefully prepared animal serum is given intravenously. If the intravenous route is contraindicated because of known sensitivity of a patient, intraperitoneal injection may be used with excellent absorption of antibodies in from 1 to 2 hours, which, with severely ill patients, is the second method of choice.

It seems curious after publication of Platou's[1] excellent work in 1923, and the more recent publication of Banks[2] that the intraperitoneal injection of serum has not been more generally used. The risk of reactions and shock is not greater than from intramuscular injection. It seems to be the general belief that there is considerable risk from intraperitoneal injection of perforating the bowel and causing peritonitis. This risk is apparently negligible when the injection is properly carried out, and is certainly less than that of delayed serum absorption in desperately ill patients.

There seems to be the general belief, also, that serum injected intramuscularly is retained in the body longer than when the serum is injected intravenously. This is a misconception. Once the peak of absorption has been reached, the serum disappears with the same rapidity as after the same level resulting from intravenous administration. However, it is true that if it is necessary to maintain a high level of antibodies in the circulating blood, and if repeated intravenous injections of serum are contraindicated, the level can be maintained with greater safety by multiple intramuscular injections.

The slowness of absorption of serum after subcutaneous injection makes this a poor method of administration even for prophylaxis.

It is obvious that an ideal therapeutic serum would be one of excellent therapeutic potency, concentrated in small volumes, which could be injected intravenously without any risk of untoward reactions, even when the injections must be repeated. Unfortunately this ideal has not yet been reached with animal serums, even though modern methods of

refining serums have resulted in products much less dangerous than previously employed. The number of instances of shock have been greatly reduced, as well as attacks of serum sickness.

Before injecting an animal serum intravenously, it is imperative to test the individual for hypersensitivity. A drop of normal serum from the same animal species should be injected intracutaneously or instilled into the conjunctival sac. In hypersensitive persons a wheal will form at the site of the cutaneous injection or marked inflammation of the conjunctiva will develop. The eye test is the more sensitive of the two. If hypersensitivity is present, at first a very small dose of the therapeutic serum, beginning with a hundredth or tenth of a cubic centimeter, should be injected subcutaneously. Gradually increasing doses can be given every twenty or thirty minutes, and if no reactions occur the intramuscular route can be used until the full therapeutic dose has been administered.

There are several therapeutically efficient human serums to be discussed later, which, when properly prepared, can be administered intravenously in large amounts, as extensive experience has shown, without fear of causing severe reactions, and with only the occasional occurrence of a mild or moderate reaction.

In addition to the specific treatment, all the accepted methods of general treatment should be carefully carried out, including quiet and protection of the patient, the provision of sufficient rest and sleep, good nursing care, special attention to proper nourishment, the prevention of dehydration, acidosis or alkalosis and avoidance of hypostasis.

Scarlet Fever

There are two serums available for the treatment of scarlet fever, convalescent scarlet fever serum (human) and scarlet fever antitoxin (animal). In recent years my interest has been concentrated on the study of the effectiveness of human convalescent serums, including that of scarlet fever.

Convalescent scarlet fever serum is prepared from blood obtained from individuals recently recovered from scarlet fever and up to a period of four months after the onset of the disease. The serum from thirty or more individuals is pooled so as to produce a polyvalent serum. Only Wassermann-negative serum is used, and care is taken to prevent even a faint trace of hemolysis. The regulations of the U. S. Public Health

Service are carefully followed, including sterility tests, and safety tests on animals.

Convalescent scarlet fever serum is therapeutically efficient and when administered early in the disease in sufficient quantities will cause subsidence of the disease in from 12 to 24 hours in 75 to 85 per cent of the individuals treated, and somewhat slower, less complete results in most of the remainder.[3, 4, 5, 6, 7] These results refer to the intravenous injection of serum within the first 36 hours after the onset, and are frequently truly dramatic, with the conversion of a desperately sick, toxic child into a convalescent one. Toxicity disappears, temperature drops an average of three degrees Fahrenheit, and not infrequently reaches normal. Vomiting and diarrhea, when present, disappear, the rash begins to fade and the usual complications are reduced to one-third in number and are less severe in intensity when they do appear.

This human serum has the advantage that it can and should be administered intravenously with practically no risk of causing untoward reactions. In an extensive experience in different parts of this country not a single instance of anaphylactic shock occurred. Sensitization to subsequent injections of human serum apparently has not been produced, and mild, delayed serum sickness occurs in not more than one-half to one per cent of the patients.

Usually only one intravenous injection is required to obtain these results when the serum is administered early in the disease and before complications have developed. If, however, complications are already present, or if the patient is brought to the hospital in the later stages of the disease, several injections may be needed at one or two day intervals.

The intravenous dosage is 20 cc. in children up to the age of five; 40 cc. in those from five to ten years; 60 cc. in those from ten to fifteen years, and 80 to 100 cc. in large adolescents or adults. Similar but less rapidly occurring improvement can be obtained from intramuscular injections, but the dosage should be definitely larger.

Although the pooled serum contains both isoagglutinins, there need be no fear from the intravenous injection of incompatible agglutinins, as has been demonstrated thousands of times. Whereas the danger of injecting incompatible cells is well known, this does not apply to the injection of agglutinins. This was also brought out recently at the meeting of the American Human Serum Association, including some studies

in our laboratory, which demonstrated that even after the injection of large quantities of incompatible serum, the incompatible agglutinins disappeared from the circulation immediately.

It has been demonstrated in some studies with Elizabeth Moore[8] that convalescent scarlet fever serum contains an appreciable amount of bactericidal substances against Group A hemolytic streptococcus, as well as antitoxin to erythrogenic toxin. Opsonins and antistreptolysin are also present.

The amount of antitoxin present in convalescent scarlet fever serum is small (averaging about 10 units per cc.) as compared with the antitoxic content of scarlet fever antitoxin (animal). Therefore, the amount of antitoxin in the doses of convalescent serum which have been described is much less than when animal antitoxin is used. Since the therapeutic response to convalescent scarlet fever is as good as or better than that to large doses of animal antitoxin in the experience of Top[9] and others,[3, 4, 5, 6, 7] this efficiency must be due to bactericidal and other antibodies which are present in convalescent serum and not present in animal antitoxin, as shown also by Platou and Dwan.[10]

Animal scarlet fever antitoxin will also produce excellent therapeutic results, and several commercial serums are available which are superior to those previously produced, in that severe reactions and delayed serum sickness occur in a smaller number of individuals. There remain, however, in using these preparations, the risk of sensitizing the individual to animal proteins and the danger of anaphylactic shock from intravenous injection. Therefore, they are rarely injected by this route. It is possible, however, to inject them intraperitoneally resulting in quite rapid absorption with no more risk of reactions than that from intramuscular injection, as demonstrated by the clinical work of Banks.[2]

The question not infrequently arises as to whether all patients with scarlet fever should be treated with specific serum therapy, or whether this should be reserved only for the severely ill. This question cannot be answered dogmatically, and undoubtedly there will be a great difference of opinion. Many factors enter into making a decision of this sort.

In general, scarlet fever does not occur in as severe a form today as previously, although occasionally grave forms of the disease still are encountered. Not infrequently, attacks that appear mild at first become severe, and at other times serious complications develop during the course of an otherwise mild scarlet fever. Unless the disease is aborted

by treatment, some toxemia, even in those mildly or moderately ill, will persist on an average of from three to five days.

Since the disease can be cut short in its earliest stages by specific serum treatment, and the risk to the patient of the development of a severe form of the disease, of complications and toxemia, can be reduced, it seems logical, though it may not always be practical, to give serum to every patient with scarlet fever, regardless of the severity of the attack.

In scarlet fever, hemolytic streptococci cause damage not only by the erythrogenic toxin which they produce, but apparently by other toxins as well, and also by direct invasion of tissues. It has been believed by some that antitoxin for erythrogenic toxin is not always sufficient to produce passive immunity against hemolytic streptococci which cause scarlet fever, since this serum is deficient in bactericidal substances. Passive immunity can be secured for a period of ten days to two weeks with intramuscular injections of convalescent scarlet fever serum when children are accidentally exposed to scarlet fever and there is fear of their developing the disease. Studies have shown that only 1 or 2 per cent of exposed children, who have been passively immunized, will develop scarlet fever, instead of 10 or 15 per cent which can be expected without this prophylactic injection. Those who do develop the disease usually have only a mild or modified scarlet fever.

It was only natural for sulfanilamide to be tried in the treatment of scarlet fever. Unfortunately, the results reported are not as good as those in other streptococcal infections. There is general agreement in the publications that sulfanilamide produces no benefit during the acute, toxic stage of the disease and does not reduce the toxicity nor shorten this stage of the illness.[11] Some reports[12, 13] state that it reduces the likelihood of complications and their severity, whereas in other reports[11, 14] it is stated that even this does not occur.

A word should be said for the combined use of the sulfonamide group of drugs with convalescent scarlet fever serum. It has been shown in a number of experimental investigations in other infections that the sulfonamide group and any specific serum have a synergistic action,[15, 16, 17] that is, the combined effect of the two is greater than the sum of the effects of these substances when each is used individually. It is suggested that in patients with severe complications both the drug and serum should be used together.

It has been found that convalescent scarlet fever serum is of con-

siderable value in treating various types of severe hemolytic streptococcal infections in conditions other than scarlet fever. This also has been true in our experience. Benefit has followed the use of convalescent scarlet fever serum where severe streptococcal infections, including blood stream infections, have not yielded to sulfanilamide, or where the patient could no longer tolerate the drug. Out of this experience has arisen the practice of administering both sulfanilamide and serum simultaneously in such serious conditions as streptococcal peritonitis, meningitis, and pneumonia. It is also necessary to give adequate operative treatment of all local sites of infection, such as mastoiditis and osteomyelitis, since serum or sulfanilamide cannot give the best results without essential surgical care of the original or any secondary feeding focus of streptococcal infection.

Measles

In recent years the prevention of measles by a number of passively immunizing agents has received increasing attention and use. Whereas there is no direct method of producing a lasting active immunity to measles this can be accomplished to a certain extent indirectly.

The first study in this country of the use of convalescent serum in the prevention of measles was carried out by William H. Park,[18] and as a result of his work and that of others the efficiency of this procedure has been demonstrated in large groups all over the world. In recent years, laboratories have been established in a number of large cities for the preparation and distribution of convalescent measles and other serums.

The blood is obtained from adolescents and adults recently recovered from measles, and at intervals up to four months after the onset of the disease. Serum from thirty or more individual bleedings is pooled and processed as already described.[6]

To obtain maximum protection serum should be injected intramuscularly, if possible by the fifth day after the child has been accidentally exposed and not later than the seventh. Because this is a human serum, its intramuscular injection is not accompanied by any danger, and local or general reactions are extremely uncommon. When the proper dose of serum is used, the disease will be either prevented or modified in from 98 to 99 per cent of the children, with no measles developing in from 60 to 80 per cent. Failure, i.e., unmodified measles, will occur in from 1 to 2 per cent.

When the disease which develops has been modified, the attack is mild and of short duration; very little if any toxemia is present; the rash is diminished in extent and severity or even absent, Koplik spots are either absent or seen with difficulty, and complications are extremely uncommon. Modified measles may be so mild that it will not be recognized unless one is familiar with it.

An important characteristic of an attack of modified measles is that it confers an active immunity, which persists for years, perhaps for life. This is true if the disease has not been too greatly modified, and for a strong active immunity there must be a detectable eruption. Following some extremely mild attacks of modified measles, after subsequent exposures, some children have developed a second attack of measles, but so far as is known each of these has also been mild.

Convalescent measles serum cannot be standardized at present with any laboratory procedure. Dosage has to be determined by experience.

For prevention, no child or infant should receive less than 5 cc. intramuscularly. Our latest information leads us to recommend 10 cc. for children from the age of three to ten, 15 cc. for older children, and 20 to 40 cc. for large adolescents or adults.

Since measles is a serious disease in infants and children up to the age of three (with a mortality rate from complicating pneumonia and other complications of about 5 per cent), we believe that the attempt should be made to prevent the disease completely in exposed individuals of this age group. This should be done also in all exposed children otherwise ill, or recently recovered from an illness, or undernourished. Children in these special categories should receive a somewhat larger amount of serum.

In healthy children five years old or older, it is probably advisable not to attempt to prevent the disease completely, but merely to modify it, in order to secure a permanent active immunity, with very little risk from the mild, modified attack.

For modification half the above doses should be administered up to and including the seventh day of exposure. The full dose given on the eighth or ninth day of exposure at times will modify the disease. After the ninth day of exposure intramuscular injections of this dose cannot be expected to have any effect on the course of the disease.

In hospitals and in children's institutions where exposure to measles has occurred the aim is always for complete prevention of the spread of

secondary cases. As already stated, one cannot obtain 100 per cent protection. At least a few children will develop modified or occasionally unmodified measles. One can prevent, however, general spread of measles, and safeguard against the general development of unmodified measles with its attendant dangerous complications.

Other materials have been used in measles prophylaxis. Pooled normal serum, obtained from individuals who some time previously have recovered from measles, is efficient when the dose is four times that of convalescent serum. Whole blood, obtained from parents or other adults, and injected immediately, is efficient but should be used in eight times the dose of convalescent serum, since serum forms only about one-half the volume of blood. The globulin fraction of pooled normal, adult serum or plasma,[19] and of pooled ascites fluid[20] and the placental globulin fraction in corresponding doses,[21] have proved to be efficient.

Formerly, it was thought that since measles is a virus disease, once its earliest manifestations had developed, it would be impossible to modify its course by the therapeutic use of serum. At the Willard Parker Hospital, New York, Kohn, Klein and Schwarz[22] demonstrated that 50 cc. of convalescent measles serum administered intravenously to children who are in the pre-eruptive stage of measles, showing Koplik spots, will mitigate the disease in about 85 per cent (25 children treated), so that, in brief, the resulting disease may be characterized as a mild, one-day illness. Similar results were reported by Levinson and Conner[23] at the annual meeting of the American Academy of Pediatrics in 1938. The importance of such observations is that many children already seriously ill with diphtheria or poliomyelitis, for example, who are discovered to be developing measles, can be spared the added risk of a severe attack of the unmodified disease.

About the treatment of measles after it has reached the eruptive stage, which should be the main topic in this section, not very much can be said. There has been no clear-cut evidence presented that once the eruption has appeared, convalescent serum will produce any demonstrable benefit. None of the publications seems convincing, and in light of the results described above of treatment in the pre-eruptive stage, one could not expect benefit from the comparatively small doses mentioned in the reports of treatment of active measles. We do not recommend the use of convalescent serum after the eruption has appeared.

Chicken Pox

Convalescent chicken pox serum has been used in an attempt to prevent this disease, and also therapeutically. Unfortunately, the experience of others and the trial at the Willard Parker Hospital indicate no efficiency in either prevention or treatment.

Diphtheria

Active immunization against diphtheria is so simple and has proved so successful that diphtheria must be considered today a preventable disease.

The treatment of active diphtheria, when it does develop today, is practically the same as it was after diphtheria antitoxin became generally available, except that better, more refined and safer antitoxic serums are now generally available.

In the opinion of many, diphtheria is going through a cycle of decreasing severity. Whether diphtheria goes through these natural cycles, or whether widespread active immunization, better hygienic conditions or other factors are responsible, is not clear. Even today occasional cases of severe or malignant diphtheria occur. It is particularly imperative that serum should be administered as early as possible, and in sufficient amount in one dose. Enough serum administered early is much more valuable than larger amounts given later in divided doses. In severe attacks of laryngeal or malignant diphtheria, part or all of the serum should be given intravenously, unless the individual is sensitive to horse serum when the injection should be made intraperitoneally, absorption being much more rapid than by the intramuscular route.

The minimum dose in an early attack of faucial diphtheria of average severity is 10,000 units intramuscularly. Large or older children should receive more, and individuals with the severest form of the disease should receive 40,000 to 60,000 units of antitoxin, all of it or half of it intravenously.

In recent years, Ramon[24, 25] and his co-workers have been using and recommending a type of therapy which they call sero-anatoxitherapy, meaning combined therapy with antitoxin and toxoid (anatoxin). They claim for this method that it does not decrease the curative effect of the antitoxin and that active immunity is stimulated by the toxoid sooner and more certainly than it would otherwise occur, minimizing complications and the frequency of relapse. This work is of extreme interest and

should be followed further. There is some evidence, from animal experiments, of a contrary nature, but this, as claimed by Ramon, might not apply to humans.

Tetanus

Much more progress has been made in recent years in the active immunization against tetanus than in passive immunization or in treatment of the active disease.

Ramon and his group[26, 27, 28] were the first to produce tetanus toxoid, and demonstrated its efficiency in animals and humans as an agent for causing a strong, durable, active immunization. Their work has been verified by many others and extended in some directions.

The production of tetanus antitoxin after a single injection of tetanus toxoid is slower than after an injection of diphtheria toxoid. It has been found that one injection is not sufficient to produce the desired response and that the spacing of the injections must be different from those with diphtheria toxoid. The second injection should be given not sooner than one month after the first. The immunity which develops does not reach the highest possible level but, nevertheless, persists for about a year. When an additional injection of toxoid is administered a year after the first one (this is called a secondary or a recall injection), it is then found that the antitoxin rapidly reaches a comparatively high level. The same level of antitoxin in animals will protect them from at least one minimal lethal dose of tetanus toxin, and will protect most, if not all of the animals, from at least one minimal lethal dose of tetanus spores injected intramuscularly.

Because of these results active immunization to tetanus is being more and more extensively practiced in some of the European armies (France and Great Britain), and for individuals whose work exposes them intimately to the likelihood of tetanus infection. Its use in civil practice seems to be spreading gradually, also.

How efficient this active immunization is or has been in the prevention of tetanus in wounded and injured individuals in the present European war, so far as can be learned, has not been reported.* This infor-

* Since this paper was written Perry[29] reported in the *British Medical Journal*, that: "Compared with the first three months of the war of 1914-18, when the incidence was about 8 per 1,000 wounded, the figure in the war is 0.45 per 1,000. It is significant that such cases as have been noted have occurred in individuals that have not been actively immunized. Among casualties of the British Expeditionary Force there has been no reported instance of tetanus in soldiers protected by means of tetanus toxoid. It is only fair to remark that a number of wounded received prophylactic doses of tetanus antitoxin subsequent to their arrival in this country—that is to say, two or three days after the infliction of the wound."

mation will be awaited with the greatest of interest.

Until this information is available, the question which is most frequently asked is: If an immunized individual (soldier or civilian) receives a wound or injury from which experience has shown tetanus is likely to develop, should the active immunity alone be relied on or should additional methods of protection be used immediately after the injury? Until more is known about this, the prevailing opinion at present seems to be that an intramuscular injection of tetanus toxoid should be given as soon as possible. It has been shown that this additional dose of toxoid will stimulate the rapid increase in tetanus antitoxin in from five to seven days, an interval which is sufficient to prevent tetanus, since it usually takes five or more days for tetanus spores to germinate, disseminate toxin, and produce the disease.

If animals previously immunized with tetanus toxoid are injected with a mixture of tetanus spores and calcium chloride, an increase in the antitoxic titer in their blood occurs slowly, if at all, and apparently only those animals survive which have a sufficient active immunity at the time of the spore injection. However, if tetanus toxoid is injected in a different muscle at the same time that the spore-calcium chloride mixture is injected, in from five to seven days a definite increase in the level of antitoxin in the blood is found and a larger percentage of animals survive. The exact level of antitoxin necessary to protect against spore injection is not known but is believed to be larger than that needed to protect against tetanus toxin.

The prevention of tetanus in injured, non-immunized individuals remains a problem. Experience in the last war demonstrated that a single injection of 1500 units of tetanus antitoxin is not sufficient. At times this will only delay the onset of tetanus which may develop weeks or months later. Tetanus was controlled best when repeated injections of antitoxin were administered at 10-day intervals for as long as seemed indicated by the condition of the wound.

At present, Ramon[30, 31] suggests that the wounded non-immunes should receive both tetanus toxoid and antitoxin so as to have the benefit of both active and passive immunization, since his animal experiments indicate that the administration of antitoxin does not slow up the process of active immunization from the toxoid. However, experimental work by Otten and Hennemann[32] leads them to conclude that the injection of antitoxin does slow up the development of active immunity from

toxoid. They suggest that antitoxin should be administered immediately for passive immunization, and an injection of toxoid be given as well. These should be followed by several injections of antitoxin and toxoid at intervals of about ten days, sufficient to maintain by passive immunization a protective level of antitoxin until active immunization will maintain this level.

Sneath and his co-workers[33] have investigated the relative degree of protection in guinea pigs by active and passive immunization against infection from the injection of standardized doses of tetanus spores mixed with calcium chloride solution. A larger number of actively immunized guinea pigs survived and were completely protected from tetanus when their blood contained 1/100 unit or more of tetanus antitoxin per cubic centimeter, than unimmunized guinea pigs which received the passive immunizing dose for humans of 1500 units of antitoxin, a huge dose for these small animals. The explanation of the difference in the experimental results with passive immunization in guinea pigs and those in man is not clear, but indicates that further studies should be made in man.

In civil practice there are certain disadvantages, such as reactions, serum sickness, and sensitization, to the administration of a prophylactic dose of tetanus antitoxin to children who have received comparatively trivial puncture wounds, and yet it is a serious responsibility for a physician to deny the child protection against tetanus.

Since the campaign for active immunization with tetanus toxoid has spread it has been found that some adults develop a relatively high titer of antitoxin in their blood, 10 units per cubic centimeter being not uncommon, with occasionally as much as 50 units.

Several years ago Schick suggested to me the preparation of human tetanus antitoxin for prophylaxis for just those instances when the physician hesitates to use an animal antitoxin. This suggestion has also been made by Hyland, as reported by Dietrich.[34] Unfortunately, it was impossible for me to secure blood from humans actively immunized and with a sufficiently high titer of antitoxin. However, should all members of the American army now being formed be immunized with tetanus toxoid, it should be possible to obtain large amounts of tetanus antitoxin (human), and it is hoped that someone will determine how efficient this antitoxin will be.

Definite advances have been made in recent years in the treatment of tetanus, once it manifests itself. This has been excellently described

and summarized in two recent articles by Dietrich[34] and Spaeth[35] and also by Vener and Bower.[36] These workers advise that an initial large dose of antitoxin be administered, preferably by the intravenous route in spite of the risk. Spaeth believes that one dose, if large enough, is sufficient. Dietrich believes that repeated intramuscular injections should be given also, so as to maintain a high level of circulating antitoxin. Since resistant spores may continue to germinate and produce toxin after the initially injected antitoxin has disappeared, repeated injections are logical. Both of these investigators agree that it is of the utmost importance to keep the patient as quiet as possible under a regime carried out by a specially trained personnel, to administer sedatives cautiously, but in sufficient amounts to prevent convulsions, to avoid all manipulations and unnecessary physical examinations if possible, to administer sufficient fluids and nourishment and not to perform lumbar punctures or administer serum intrathecally. They believe that the intrathecal administration of serum causes meningeal irritation which is harmful and that the anesthesia necessary for lumbar puncture is also harmful. Both believe that deaths have been caused by excessive serum treatment and overmanipulation. Apparently overtreatment must be avoided, nevertheless, large amounts of antitoxin must be administered.

The importance of preventing convulsions with sedatives, aside from the exhaustion which these cause the patient, is graphically illustrated by the reply of one child who recovered: when he was asked how the convulsion felt, he said, "You know how much it hurts when you have a cramp in your leg. Well, convulsions feel like that all over."

It is difficult to make a comparative evaluation of results in the treatment of tetanus, but certainly those reported by these investigators seem excellent and give hope that they can be repeated or even improved.

Bacteriophage

When it was discovered that bacteriophage would cause solution and death of bacteria *in vitro* it was hoped that this could be accomplished *in vivo*. Unfortunately, the clinical trial of many types of bacteriophage has been disappointing. Therefore, bacteriophage is very seldom used today in the treatment of bacterial infections, a further indication of its lack of efficiency.

Each phage has a specific range of activity and, as would be ex-

pected, the least efficiency is found in stock preparations. It requires several days for trained workers to prepare a specific phage, during the time when the need of treatment is most urgent. Only actively growing bacteria are lysed, resistant strains are not uncommon, and will develop if lysis is incomplete. Proteins and many other colloids inhibit lysis and inflamed areas are walled off, reducing the probability of contact of phage and bacteria. The injection of bacterial filtrates may cause a therapeutic response similar to phage. Preparations of bacteriophage contain peptones, meat extracts, products of bacterial growth and dissolved bacteria, all of which may cause physiological effects or systemic reactions.

In general blood stream infections, bacteriophage has been given intravenously by some. The initial doses must be very small, about one-tenth of a cubic centimeter, and severe, febrile and chill reactions are caused not infrequently. Gradually increasing doses are administered at intervals of several hours, and reactions may occur after any of these. Some investigators have believed that beneficial effect will follow only when reactions of this sort have been produced, and others are of the opinion that the improvement which occurs should be attributed not to the phage but to a general, non-specific reaction.

Extensive use of phage in the treatment of severe staphylococcus infections, including bacteriemia, has been made by MacNeal and his colleagues.[37] They are convinced that much has been accomplished in the treatment of a large series of patients. Although statistical evaluation is difficult, the favorable opinion of such outstanding workers must be given serious consideration.

With the recent development and use of chemotherapy in bacterial infections it will be more difficult than ever to estimate the value of bacteriophage in staphylococcus infections.

It is questionable, from the published reports, if phage has any efficacy in the treatment of bacillary dysentery.

Staphylococcal Infections

Until the recent use of sulfathiazole, one had to rely on bacteriophage, antitoxic serum and multiple small blood transfusions in the treatment of severe staphylococcus infections with or without bacteriemia. Apparently the antitoxin as developed by Dolman[38, 39] and by Ramon[40] has been of real help in treating some patients. Perhaps, under desperate

circumstances, a combination of sulfathiazole and antitoxin should be used, as it is logical to believe that these two will act synergistically, as do other similar combinations.

There is some evidence[41, 42] also, that multiple injections of staphylococcus toxoid are beneficial in the treatment of even severe acute infections. Not all observers agree about this. The beneficial results of the treatment of subacute or chronic staphylococcus infections with toxoid seem more clear-cut but here, too, there is not complete agreement of different investigators. The best results seem to be in the prevention of recurring attacks of boils by the injection of toxoid during the intervals between these attacks. Autogenous staphylococcus vaccines have a limited efficiency under these conditions, also.

Gas Bacillus Infections

As pointed out in a recent editorial in the *Lancet*,[43] the treatment of gas gangrene with antitoxin appears to have fallen in disrepute for reasons that are difficult to find. During the last war there can be little doubt that the lives of many individuals infected with *Clostridium welchii* and *Vibrion septique* were saved by means of antitoxic sera of low potency as compared with those produced today. This efficacy was both prophylactic as well as therapeutic. Since then this experience has not been much enlarged, if for no other reason, because of the infrequent occurrence of gas gangrene in civil practice.

Although more recently some excellent therapeutic results have been achieved with the use of the sulfanilamide group of drugs it would be unfortunate if an attempt were not made to improve upon these results by the use also of modern, potent sera. This is especially important since recently Henderson and Gorer[44] have demonstrated experimentally in animals infected with the organisms of gas gangrene that "there is a striking, synergistic curative action of sulfapyridine plus antitoxin." Their study indicates that in treating the disease in humans an adequate dose of antitoxin should be given intravenously at the earliest possible moment, one therapeutic dose for the suspected case, and for the established case, three to five doses combined with 6 to 9 grams of sulfapyridine daily until the infection is obviously controlled.

Anthrax

Anthrax is so uncommon in this country that unfortunately infec-

tions of the skin caused by this organism are not always recognized immediately. Early diagnosis is of extreme importance for successful treatment, as the disease frequently reaches the bacteriemic stage with great rapidity.

After many kinds of treatment of the local skin lesion, such as, excision, cauterization with chemicals, or the actual cautery, it is now generally agreed that the lesion should merely be protected and kept dry, as manipulations tend to spread the infection rather than control it.

Anthrax antiserum should be administered intravenously at the earliest possible moment in large amounts of 100 or 200 cc. at a time, after, of course, taking the usual precautions against sensitivity of the patient to the animal serum. Large injections should be repeated intravenously once or twice during the first twenty-four hours, and continued at intervals for several days until definite improvement or recovery has occurred. All observers have not obtained equally good results, but certainly some recoveries seem attributable to early, vigorous treatment.

Botulism

Although this condition is relatively uncommon in this country, it still occurs occasionally in outbreaks in small or large groups who have eaten foods containing the toxin of *Clostridium botulinum*. Under these circumstances the disease has a high mortality.

In 1934 Velikanov and Kolesnikova[45] reported an excellent clinical study of 227 cases of botulism. Of these, 146 received serum, and 81 that did not served as controls. Among the 146 that were treated, 26 died, a mortality of 18 per cent, and among the 81 not treated with serum, 76 died, a mortality of 93 per cent.

Large amounts of serum were given, each dose being from 60 to 100 cc. The best results were obtained when this treatment was given early in the disease.

Some of the most severely ill received repeated doses of serum at short intervals, a few as much as a total of 600 to 700 cc.

In several apparently hopeless cases serum was administered intravenously, and twice intraspinally in doses of 10 to 20 cc. with recoveries that were described as astonishing.

REFERENCES

1. Platou, E. S. Antitoxin in diphtheria; a comparative study of the usual methods of administration with the intraperitoneal method, *Arch. Pediat.*, 1923, *40:* 575.
2. Banks, H. S. Intravenous or intraperitoneal antitoxin treatment combined with short isolation period in scarlet fever, *Lancet*, 1936, *2:*559.
3. Hardgrove, M. The prophylactic use of scarlet fever convalescent serum, *Wisconsin M. J.*, 1938, *37:*821.
4. Hoyne, A. L., Levinson, S. O. and Thalhimer, W. Convalescent scarlet fever serum; its prophylactic and therapeutic value; a review of 2,875 cases, *J.A.M.A.*, 1935, *105:*783.
5. Hyland, C. M. and Anderson, L. R. Prophylactic and therapeutic use of scarlet fever convalescent serum, *Am. J. Dis. Child.*, 1937, *54:*504.
6. Thalhimer, W. The value of convalescent scarlet fever, measles and mumps serum in prophylaxis and therapy, *M. Clin. North America*, 1939, *23:*613.
7. Zingher, A. A simple syringe method for the transfer of blood from donor to recipient; its application in the treatment of scarlet fever and other conditions, *Arch. Pediat.*, 1914, *31:*912; and The use of convalescent and normal blood in the treatment of scarlet fever, *J.A.M.A.*, 1915, *65:*875.
8. Moore, E. and Thalhimer, W. Immunologic properties of scarlatina convalescent serum, *Am. J. Dis. Child.*, 1939, *58:* 1039.
9. Top, F. H. and Young, D. C. Specific and nonspecific serum treatment of scarlet fever, *Am. J. Pub. Health*, 1939, *29:*443.
10. Platou, E. S., Dwan, P. F. and Hoyt, R. E. Streptococcus convalescent serums (scarlatinal), *J.A.M.A.*, 1941, *116:*11.
11. French, J. O. The sulphanilamide treatment of scarlet fever, *J. Hyg.*, 1939, *39:* 581.
12. Peters, B. A. and Havard, R. V. Chemotherapy of streptococcal infections with p-benzylamino-benzene-sulphonamide, *Lancet*, 1937, *1:*1273.
13. Sako, W., Dwan, P. F. and Platou, E. S. Sulfanilamide and serum in the treatment and prophylaxis of scarlet fever, *J.A.M.A.*, 1938, *111:*995.
14. Hogarth, J. C. Para-benzylaminobenzenesulphonamide in the treatment of scarlet fever, *Brit. M. J.*, 1937, *2:*1160.
15. Banks, H. S. Serum and sulphanilamide in acute meningococcal meningitis; a preliminary survey based on 113 cases, *Lancet*, 1938, *2:*7.
16. Powell, H. M. and Jamieson, W. A. Combined therapy of pneumococcic rat infections with rabbit antipneumococcic serum and sulfapyridine (2-sulfanilyl aminopyridine), *J. Immunol.*, 1939, *36:* 459.
17. Rosenthal, S. M., Bauer, H. and Branham, S. E. Comparative studies of sulphonamide compounds in experimental pneumococcus, streptococcus and meningococcus infections, *Pub. Health Rep.*, 1937, *52:*662.
18. Park, W. H. The injection of serum or plasma from convalescent cases of measles, to prevent the development of the disease in children, *Proc. Internat. Conf. on Health Problems in Tropical America*, 1924: 908.
19. Karelitz, S. Globulin extract of immune adult serum in the prophylaxis of measles, *Proc. Soc. Exper. Biol. & Med.*, 1933-34, *31:*793; and Measles prophylaxis, *New York State J. Med.*, 1935, *35:*876.
20. Thalhimer, W. and Stillerman, M. Prevention and modification of measles with concentrated pooled ascites fluid and with its globulin fraction, *Proc. Soc. Exper. Biol. & Med.*, 1939, *42:*683.
21. McKhann, C. F. and Chu, F. T. Antibodies in placental extracts, *J. Infect. Dis.*, 1933, *52:*268; and The use of placental extract in the prevention and modification of measles, *Am. J. Dis. Child.*, 1933, *45:*475.
    McKhann, C. F. Prevention and modification of measles, *J.A.M.A.*, 1937, *109:* 2034.
22. Kohn, J. L., Klein, I. F. and Schwarz, H. The treatment of preeruptive

measles with convalescent serum, *J.A.M.A.*, 1938, *111:*2361.

23. Levinson, S. O. and Conner, J. A. The treatment of active measles with human convalescent serum, *J. Pediat.*, 1939, *14:* 268.
24. Ramon, G. La séro-anatoxithérapie antidiphtérique; son but; ses bases; premiers resultats d'ensemble, *Bull. et mém. Soc. méd. d. hôp. de Paris*, 1938, *54:*1301.
25. Ramon, G. Bases expérimentales et résultats immunologiques d'une nouvelle méthode de traitement de la diphtérie; la séro-anatoxithérapie diphtérique, *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, 1939, *97:*194.
26. Ramon, G. La vaccination antidiphtérique et la vaccination antitétanique au moyen des anatoxines spécifiques et les vaccinations associées dans la pratique, *Rev. d'immunol.*, 1935, *1:*37; L'anatoxine tétanique et la vaccination contre le tétanos, *Ann. méd.*, 1937, *42:*358; and La prevention du tétanos au moyen de la sérothérapie et de la vaccination spécifique, *Mém. Acad. de chir.*, 1938, *64:* 715.
27. Ramon, G. and Descombey, P. L'anatoxine tétanique et la prophylaxie du tétanos chez le cheval et les animaux domestiques, *Ann. de l'Inst. Pasteur*, 1927, *41:*834.
28. Ramon, G. and Zoeller, C. L'anatoxine tétanique et l'immunisation active de l'homme vis-à-vis du tétanos, *Ann. de l'Inst. Pasteur*, 1927, *41:*803.
29. Perry, H. M. Prevention of tetanus, *Brit. M. J.*, 1940, *2:*364.
30. Ramon, G. L'anatoxine tétanique et les nouvelles méthodes de lutte contre le tétanos, *Bull. Acad. de méd.*, 1939, *121:* 609.
31. Ramon, G., Kourilsky, R., Richou R. and Kourilsky, S. Essais de séro-vaccination antitétanique, *Bull. et mém. Soc. méd. d. hôp. de* Paris, 1938, *54:*1287; and Sur la séro-vaccination anatoxique et sur la séro-anatoxithérapie tétanique, *ibid.*, 1938, *54:*1442.
32. Otten, L. and Hennemann, I. P. Combined (simultaneous) immunisation against tetanus, *J. Path. & Bact.*, 1939, *49:*213.
33. Sneath, P. A. T., Kerslake, E. G. and Scruby, F. Tetanus immunity: the resistance of guinea pigs to lethal spore doses induced by active and passive immunization, *Am. J. Hyg.*, 1937, *25:* 464.
34. Dietrich, H. F. Tetanus in childhood, with special reference to treatment, *Am. J. Dis. Child.*, 1940, *59:*693.
35. Spaeth, R. A clinical study of tetanus, *Am. J. Dis. Child.*, 1940, *60:*130.
36. Vener, H. I. and Bower, A. G. Treatment of tetanus, Abstract in: *A.M.A. Program of Scientific Assembly*, 1940: 7.
37. MacNeal, W. J. and Frisbee, F. C. Bacteriophage service to patients with staphylococcus septicemia, *Am. J. M. Sc.*, 1936, *191:*170; and One hundred patients with staphylococcus septicemia receiving bacteriophage service, *ibid.*, 1936, *191:*179.
38. Dolman, C. E. Staphylococcus antitoxic serum in the treatment of acute staphylococcal infections and toxæmias, *Canad. M. A. J.*, 1934, *30:*601; *31:*1; 130.
39. Dolman, C. E. and Kitching, J. S. Staphylococcus toxin, toxoid and antitoxin, *Canad. Pub. Health J.*, 1936, *27:*529.
40. Ramon, G. and Richou, R. Sur la production rapide d'un sérum anti-staphylococcique de valeur antitoxique élévée, *Rev. d'immunol.*, 1939, *5:*427.
41. Ramon, G. L'anatoxine staphylococcique et la thérapeutique des affections due au staphylocoque, *Arch. de méd. d. enf.*, 1938, *41:*665.
42. Ramon, G. *et al.* L'anatoxithérapie spécifique des affections staphylococciques, *Presse méd.*, 1937, *45:*929; and L'anatoxine staphylococcique et son emploi dans le traitement spécifique de certaines affections dues au staphylocoque, *ibid.*, 1935, *43:*1137.
43. Editorial. Antitoxin in the treatment of gas gangrene, *Lancet*, 1940, *1:*1127.
44. Henderson, D. W. and Gorer, P. A. The treatment of certain experimental anaerobic infections with sulphapyridine and with immune sera and the problem of synergic action, *J. Hyg.*, 1940, *40:*345.
45. Velikanov, I. and Kolesnikova, M. K. Beneficial results of serotherapy in botulism, *Klin. Med.*, 1934, *12:*1807.

INFECTIONS OF THE MIDDLE EAR AND NASAL SINUSES*

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WHEN it is realized that every cold is a potential sinus involvement and that chronic sinusitis probably causes more ill-health than any other disease, it is obvious that every physician should be thoroughly familiar with the pathological changes which accompany sinusitis. The general physician is the first to be consulted; he should, therefore, be in a position to give authoritative advice. Yet, in the past, comparatively little has been known about the physiology of the nose, the pathology of sinus infection, the effect of constitutional conditions upon the function of the nose, and the possibility of allergic influence has not always been sufficiently considered.

ANATOMY AND PHYSIOLOGY

The nose is an extremely complicated anatomical structure. No two nasal chambers are exactly alike; no two can be expected to act alike, even in the same individual. Nor do any two patients respond identically, either constitutionally or locally, to nasal therapy.[1] The function of the nose is so controlled through the nervous system that any abnormality in any portion of the body, from the skin to the heart, may have a decided bearing on it.

Small wonder, then, that there is considerable confusion on the subject in the mind of the layman, the general practitioner and even the rhinologist. I believe Ballance has well stated the case when he says, "Once the pathology is understood, differences of opinion as to therapy should disappear."[2] To further this better understanding, let us briefly review some of the high lights in the anatomy and physiology of the nose.

Chambers: The nose consists of two chambers, separated by the septum and surrounded by cavities connected with it by very small open-

* Given October 21, 1940 in the Graduate Fortnight of The New York Academy of Medicine.

ings, called ostia, which render the passage of air from the nose into the sinus and drainage from the sinus possible.

Turbinates: There are three turbinate bodies situated one above the other in the lateral wall of each chamber, dividing this wall into three compartments called respectively the superior, middle and inferior meatus. The turbinates have the most abundant blood supply of any part of the nose; they have much elastic and smooth muscle fiber and large cavernous sinuses, giving them the characteristics of erectile tissue and rendering them particularly responsive to all types of sympathetic nervous system reactions, to inflammation or allergies, to thermal, chemical (either local or general), emotional and constitutional changes. Their function is to direct properly, warm and moisten the inspired air. Because this function is maintained by the coördinated action of both sensory and involuntary nerves, any constitutional dyscrasia may cause functional nasal changes and local symptoms which may simulate sinus disease. "Such symptoms as nasal obstruction in hot dry rooms; a watery discharge in cold weather; and, during adolescence, the dropping back into the throat of secretions and the obstruction of the nose on the dependent side are physiological responses which need not necessarily be the result of pathology in the nose."[3] It is well to look for causes other than nasal, when the patient complains of a postnasal discharge which is not excessive, especially where there is no pronounced tracheal cough. Fifty per cent of such cases are probably allergic. Other possible causes are endocrine imbalance, intestinal stases, anemia, syphilis and diabetes. When the postnasal discharge is abundant and accompanied by the characteristic tracheal cough, the cause is usually sinus infection. As the turbinates are important in directing the air currents to the nasopharynx, due consideration must be given these facts where operative interference is contemplated.

Position of Ostia–Inferior Meatus: The lacrimal duct empties into the inferior meatus (below the inferior turbinate), hence the futility of treating nasal conditions with drops put into the eye.

Middle Meatus: Into the middle meatus (below the middle turbinate) empty most of the sinuses, i.e., the antra, frontals and anterior ethmoids; therefore, the anatomy of the middle meatus is the most important insofar as sinus involvement is concerned. Drainage from all sinuses depends principally on ciliary action. The frontal sinus drains *down-hill* from its lowest point by a long, often tortuous, passage

through the ethmoids into the middle meatus. The anterior ethmoids drain *down-hill* into the middle meatus at nearly the same point as the frontal and antrum. The antra empty into the middle meatus through one or more openings situated in the uppermost part of the antral cavity, necessitating *up-hill* drainage. Here any interference with the action of the cilia renders drainage impossible.

Superior Meatus: The posterior ethmoids empty into the superior meatus (below the superior turbinate); while the sphenoid empties into the space above and posterior to the superior turbinate. The sphenoid is drained by an opening situated high on its anterior surface, necessitating *up-hill* drainage; here, too, the action of the cilia is of prime importance.

It is thus evident that all the sinuses drain down-hill excepting the antrum and sphenoid. The antrum is the most common site of infection, the sphenoid the rarest. The probable explanation is that the anatomical structures surrounding the ostia of the antrum are far more liable to be deformed, thus obstructing the ostia and impeding ciliary action. For this reason the antrum is the sinus most likely to require aid to drainage.

Drainage: A large part of the drainage from the sphenoids and posterior ethmoids goes down the throat. Most of the other sinuses, by reason of ciliary action, would naturally drain down the throat also, but the action of blowing the nose directs a certain amount anteriorly. The postnasal and the lymphatic drainage from an infected sinus causes the tracheal cough so characteristic of sinus infection.

Causes of Ostial Obstruction: If the formation of the nose were perfect, sinus infection would occur only as a result of swimming, ill-advised local applications or allergy. Since such perfection is rarely attained, we shall find that about 85 per cent of all x-rays of the nasal sinuses show some degree of involvement. A septal ridge or spur which projects into the middle meatus, especially in the anterior part, crowding the middle turbinate against the outer wall and so interfering with the function of the ostia of the antrum and other sinuses, is almost certain to result in poor drainage from these sinuses, with consequent chronic infection. When there is obstruction of one side of the nose by a deviated septum, there will be a compensating enlargement of the turbinate on the opposite side as a result of improper aeration. A middle turbinate which has become greatly enlarged as a result of improper aeration, a misplaced ethmoid cell, or persistent allergic reaction, will most certainly obstruct

the ostia by its size alone, and sooner or later infection will occur. In such a case, it is necessary either to relieve the underlying allergy, improve air circulation or create better drainage for the sinuses involved.

Respiration: When the nasal ostia are unobstructed, inspiration causes a negative pressure in the nose and sinuses; expiration, a positive pressure. It has been demonstrated that when, because of obstruction of the ostia, pressure in the nose and antra differs, secretion will generally be found in the antra. Insufficient ventilation of the nose, with the resultant mouth-breathing, also causes poor drainage from the sinuses.

Absorption: Experimentally, it has been shown that dyes placed in an acutely inflamed sinus, of which the ostia are completely blocked, will appear in the urine within fifteen minutes. This will give some idea of the absorbing power of the mucous membrane in inflamed sinuses when the ostia are blocked by acute swelling or chronic thickening. It also explains why the sinus patient seems more ill than one with an ordinary cold.

Cilia: The cilia constitute the greatest protection which the nose possesses. The entire lining membrane of the nose and sinuses is supplied with these hair-like processes which wave toward the ostia and the nasopharynx. Over the cilia is a tenacious layer of mucus which tends to catch foreign particles and invading bacteria and is moved onward by the cilia. The introduction into the nose of anything which interferes with the ciliary action or the mucous coat, impairs the natural protection supplied by the mucous membrane. For this reason the habit of spraying the nose with antiseptics is obviously not to be recommended. Unobstructed ostia and free ciliary action are all-important and must be maintained or reëstablished at all times. In acute infections, swelling of the membrane in the ostia halts normal drainage; hence, anything which tends to shrink this membrane is an advantage. Our choice of drugs—of which we shall speak later—must be confined to those which do not interfere with ciliary action. Thick pus retards or stops the action of the cilia, and should be evacuated by means of lavage. Since ciliary action ceases at temperatures below 53° and above 109°F, the use of too hot or too cold solutions or vapors is contraindicated.

Allergy: In any nasal syndrome, allergy must first be considered as a possible cause. Hansel gives statistics indicating that in about one-third of the cases seen by the rhinologist, the symptoms are primarily allergic.[4] Such cases can usually be determined by a careful preliminary history.

Negative skin tests cannot always be accepted as ruling out any sensitivity. When allergy is the underlying but undiscovered cause, the result of any and all nasal procedures is likely to be unsatisfactory, and it will explain many disappointing results of surgery. Allergy can simulate every nasal symptom of which a patient may complain. He may have what he calls a "cold," although a careful history will reveal that these "colds" come suddenly, with sneezing and are of but one or two days' duration; or he may have a "chronic cold" which strongly suggests sinusitis but may actually be allergic. Any medication in a nose of this type is likely to increase the symptoms. Operations are contraindicated unless the allergy is also treated; many nasal operations would prove unnecessary if the underlying allergy were treated first. On the other hand, the perennial types of allergy may bring about permanent changes in nasal membranes rendering them more susceptible to infection; here operation for the cure of infection should be undertaken. In cases where treatment of the allergy, per se, fails to give adequate relief, the removal of hypertrophied tissue will help, by improving drainage and ventilation.

Now that we have an up-to-date outline of the physiology and pathology of the nose and nasal sinuses, let us consider briefly the pathology and treatment.

Pathology: If the function of the nose is unimpaired, a "cold" is self-limited and will disappear in a few days. If the symptoms are due to an allergic condition, it will clear up in one or two days unless there is a superimposed infection or too much medication to which the patient is sensitive. A cold which persists longer than a week, with continued congestion of one or both nostrils, excessive secretion, cough or recurring temperature, with or without pain, is strongly suggestive of sinus involvement. At the beginning of a cold, there is an acute congestion of all nasal membranes, the ostia swell and drainage becomes difficult. At this point anything that can be done to improve the general resistance and open the nasal ostia by shrinkage will facilitate prompt recovery. When, in spite of all efforts, the ostia do not open, suppuration follows. If this stage is prolonged by failure to aid drainage by lavage through the normal opening, there is infiltration of the connective tissue and permanent hyperplasia of the lining membrane. Unless drainage is now obtained, degeneration of the mucosa, together with polypoid and cystic formation occurs. This condition can be cured only by removal of the diseased tissue; if this is not done, the patient must tolerate the symptoms

of chronic sinusitis. Hence the importance of recognizing the symptoms of acute sinusitis and of not allowing them to become chronic.

Antra: My personal experience has led me to believe that the antrum is the keystone to most nasal pathology and the best point of attack. In support of this thesis, I present the following statistics obtained from a cross section of one thousand case histories taken from my private practice. These histories cover a twenty-five year period, limited to ear, nose and throat work, and are drawn from approximately twenty-thousand records. Of the thousand cases studied, 474, or 47 per cent, gave no history of nasal disturbance; the remaining 526, or 53 per cent, showed nasal involvement in the following proportions:

191, or 36 per cent were due to causes other than sinus infection.

335, or 64 per cent, were due to sinus infection.

The distribution of these 335 cases is shown in Table "B."

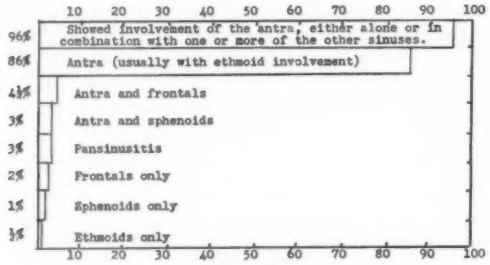

10 20 30 40 50 60 70 80 90 100
96% Showed involvement of the antra, either alone or in combination with one or more of the other sinuses.
86% Antra (usually with ethmoid involvement)
4½% Antra and frontals
3% Antra and sphenoids
3% Pansinusitis
2% Frontals only
1% Sphenoids only
½% Ethmoids only
10 20 30 40 50 60 70 80 90 100

TABLE "B"
Chart Showing The Incidence of the Involvement of the Various Sinuses.

From these statistics the importance of the antra as retainers of nasal infection appears self-evident. Granting this, it is also evident that if acute antral infection is prevented from becoming chronic there will be far less involvement of the other sinuses through extension of infection. The above figures show how rarely the ethmoids are involved without accompanying involvement of the antra, and vice versa. In such combined infections, whether acute or chronic, treatment of the antra will do much to clear up the ethmoids but treatment of the ethmoids will never cure the antra.

Because of the anatomy of the nasal chambers, treatment of the antra will almost always tend to clear up any other sinuses simultaneously involved. In the acute stage, shrinkage of the middle meatus is advisable; this can be done by means of a pledget of cotton moistened

with a mild cocaine solution, and the use of ephedrin (1 per cent) in normal saline in the form of drops. As the acute stage passes and the secretions become thicker, it is advisable to aid drainage by lavage of any obstructed sinus. Such lavage can best be accomplished, with the minimum of trauma, by passing a cannula through the normal or accessory opening. In the chronic stage of pansinusitis, operation on the antra will do more to clear up the other sinuses than any other procedure.

Medication: A wide variety of drugs has been tried in nasal treatment and experience has taught some very important lessons in this field.

Dilute ephedrin, a one per cent solution in normal saline, interferes as little as any known substance with the natural function of the mucous membrane. It is excellent to relieve congestion and to assist sinus drainage. It should be used, without preservatives of any kind, in the form of drops (one-half inch of the solution in an eye dropper) placed in each nostril with the head well back. It should not be used too frequently, as some patients develop an intolerance for this drug. Increased congestion following its use indicates either the existence of such an intolerance or of a sinus which needs attention.

Benzedrine inhalant will give considerable temporary relief but used too frequently will produce bad constitutional reactions. It has, however, no effect on the cilia.

Cocaine in a weak solution (not over 5 per cent) has no deleterious effect upon the cilia. In the majority of cases its use by direct application, alone or in combination with ephedrin, is most effective in shrinking the ostia. However, inquiry should always be made regarding the patient's reaction following its use, since cocaine may cause severe headache and depression and some people have a decided idiosyncrasy for it. Whenever a patient reports headache or malaise following treatment, the cocaine is sure to be the cause. In all such cases, a substitute, such as pantocaine (2 per cent) and ephedrin (1 per cent) should be used.

Normal salt solution does not interfere with ciliary action but the habit of daily irrigation with this solution will in time produce definite changes in the mucous membrane. It is also well to note that after nasal operations dry treatment is preferable to wet, as moisture causes edema of the new tissue.

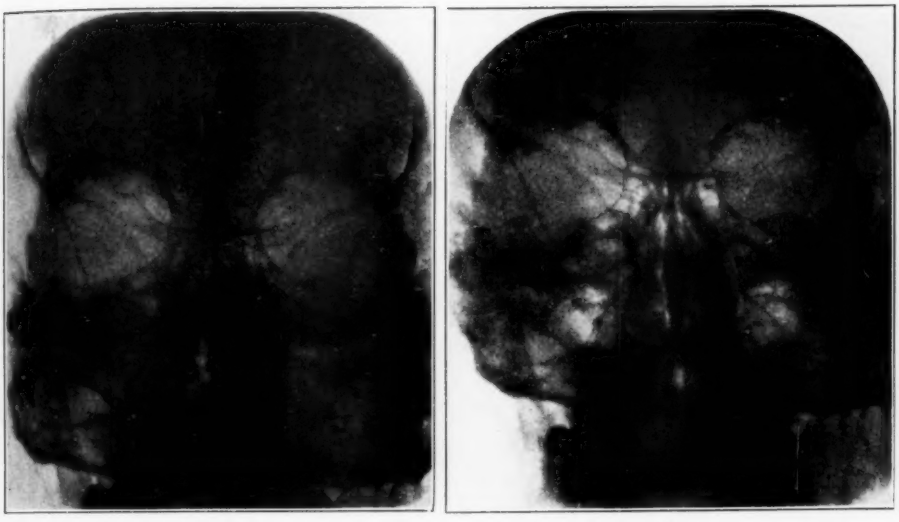
Argyrol and neosilvol used frequently, or over an extended period, will produce argyria. Patients often exhibit the characteristic silvery,

Figure 1: A case of chronic pansinusitis before treatment

Figure 2: After treatment: the same patient as Figure 1; 15 months after double radical operation on the antra showing the beneficial effects on the other sinuses

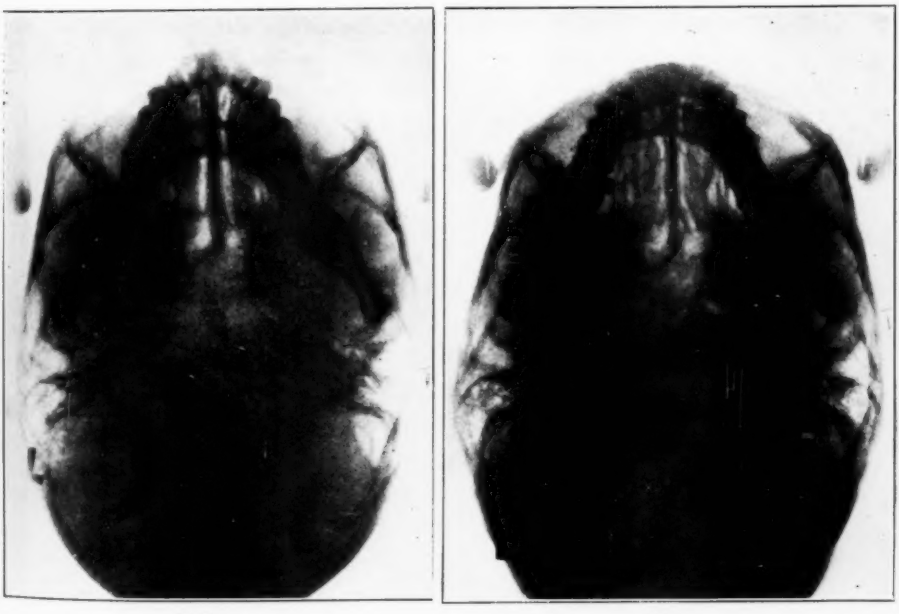
Figure 3: Before treatment: an acute pansinusitis which was cured in three weeks by lavage through the normal openings; four drachms of thick pus were originally found in each antrum

Figure 4: After treatment: the same patient as Figure 3; two months later, showing that the antra cleared



Before After

Figures 5 and 6: The same patient as Figure 3; showing that the ethmoids and frontals cleared after treating the antra



Before After

Figures 7 and 8: The same patient as Figure 3; showing that the sphenoids cleared after treatment of the antra

dusky skin, black turbinates and nasopharynx, black streaks down the pharynx (I have seen the interior of the larynx black) following the prolonged use of argyrol. The appearance of argyria may possibly be delayed months after the drug is discontinued but once it appears it is permanent. Since argyrol has no bactericidal properties when used in a pack, any beneficial result obtained is due to osmosis. In other words, the patient's nose is washed in its own secretions and shrinkage is obtained by drawing fluids out of the tissue. Hypertonic saline solution would accomplish the same result without danger of argyria.

Petrolatum does not interfere with ciliary action but it lies on the mucous coat and by its additional weight slows the progress of this coat toward the nasopharynx. This is true of any oily solution. It has been shown that drugs dissolved in oil do not penetrate the mucous coat to reach the epithelium; phenol and iodin are so firmly held in oil that they are rendered inert. Mineral oils when used in the nose have been known to produce lipoid pneumonia, especially in children; vegetable oils are less harmful. As a matter of fact, oil should be used only in chronic crusting conditions where the cilia are not functioning.

The constant use of any of the popular sprays for the nose, containing menthol, eucalyptol, camphor, petrolatum, will produce definite changes throughout all layers of the mucosa and is not to be recommended.

X-ray treatment of sinusitis is still debatable; some men claim excellent results in the acute stages of infection. The literature does not confirm this.

Diathermy is reported to cure when used twice a week for a month, but I have seen it increase the pain in acute frontal sinusitis, and no confirming articles on the subject have appeared in the literature.

Many other treatments have been advocated for use daily, or twice weekly, with the claim that cases so treated recover in a month's time. One cannot help echoing Hoople's question whether "these treatments do not prolong the condition to make it last so long."[5]

Chemotherapy in nasal pathology: Recently chemotherapy has entered the field of nasal therapy but so far there is very little to be found in the literature on the subject of its use in sinus infection.

I have used chemotherapy on very severe aural and nasal infections, which seemed to be getting out of control and the result has been miraculous. I, personally, have not seen, in the treatment of sinusitis, any

flare-ups following the discontinuance of the drug, such as frequently occur in mastoiditis. However, at the recent American Medical Association meeting in New York City, Dr. Shambaugh reported two patients on whom chemotherapy was used, who apparently recovered, yet later developed meningitis and died. To my mind, this report constitutes a warning rather than a contraindication to the use of the drug. I have also tried chemotherapy on cases of chronic nature, with thick pus in the antral washings and thickened membrane in the sinuses; in these cases I have had very negative results. Apparently the drug works best, in sinusitis, in the presence of a fulminating infection. According to Shambaugh's report, it may have a masking effect, just as in mastoiditis, and will therefore need careful watching even after the patient is clinically well. The best method of checking on this masking effect is by means of x-rays. I have seen patients, clinically recovered from mastoiditis and frontal sinus infection whose x-rays showed progress in bone destruction. It is safer, in the presence of an undrained focus of infection, not to rely too much on chemotherapy alone.

Chemotherapy in aural pathology: "My experience leads to the conclusion that chemotherapy is of decided advantage in the treatment of acute purulent otitis media provided it is started early before the condition of the mastoid has progressed to softening of the bone. Where such softening has occurred, the use of chemotherapy so changes the clinical picture as to make it almost impossible to determine the presence of progressive bone destruction and to ascertain the advisability of operating. With chemotherapy the clinical picture has ceased to be the reliable guide to pathological conditions in the mastoid, and roentgenograms have become an invaluable aid and at times afford the only diagnostic sign. In doubtful cases it is well to stop administration of the drug for a time in order to get the true clinical picture.

Chemotherapy is indicated if, at the time of myringotomy, the fundus has a very bad appearance or if myringotomy reveals pus or fluid under great pressure, with or without the presence of mastoid tenderness and regardless of the results of culture.

If the fundus does not seem to be in bad condition and the pressure on myringotomy is not great, chemotherapy may be deferred; but, if subsequently the ear does not improve promptly, chemotherapy should be started at once, regardless of the culture. If complications intervene, the drug should be used immediately regardless of culture,

but never without removing the focus.

After mastoidectomy the wound should be free from pus and the temperature should return to normal within two or three days. If chemotherapy is given during this early postoperative period and if it produces persistent temperature accompanied by symptoms simulating meningitis or labyrinthitis, the picture is very alarming. For this reason, it is preferable *not* to give the drug postoperatively in *uncomplicated* acute mastoiditis.

The drug is not effective in uncomplicated *chronic* mastoiditis. Its efficiency is lessened in cases in which there have been previous severe attacks of acute purulent otitis in the same ear.

From a series of 793 cases of acute purulent otitis media, treated during the past three years, 50 per cent of whom were given chemotherapy, I draw the following conclusions.

If chemotherapy is given early before bone destruction occurs, the duration of discharge and the number of mastoidectomies is diminished by about 50 per cent.

When the clinical picture strongly suggests mastoidectomy, it is safer to operate.

After uncomplicated mastoidectomy, it is better *not* to give the drug.

Complicated mastoiditis requires intensive chemotherapy.

At times it is necessary to stop the drug in order to obtain the true picture, as the middle ear may respond favorably to the drug while progressive bone destruction is taking place in the mastoid."[6]

Sulfathiazole should *not* be used in meningitis secondary to ear, nose and throat infections as it is not absorbed into the spinal fluid.

A general rule to follow in the administration of the drug is that when there is no response in 48 hours to chemotherapy *properly given*, some additional help must be obtained. One of the apparent causes for failure of chemotherapy in such cases, is lack of development of antibacterial antibodies on the part of the host. However, when indicated, antibody determination can be made.[7] The administration of the drug may be stopped or delayed for a few days, to allow time for the formation of antibodies but this will not be found as satisfactory as the use of immune sera and immuno-transfusions. Any one of these, or a combination, may be sufficient to insure the successful increase of antibacterial antibodies and therefore a better response to the drug.[7]

Of the various forms of the drug in present use, sulfanilamide appears to be specific for the Streptococcus hemolyticus. Sulfapyridine has a broader usefulness; it is efficacious in pneumococcic and in staphylococcic infections as well as in streptococcic. It may produce toxic symptoms which are often severe, sometimes simulating meningitis so closely as to be alarming when it is used in the therapy of nose and ear infections. It should, despite this, be used in true meningitis. Sulfathiazole, although it frequently causes rashes, seems to be less generally toxic; it has an excellent effect on pneumococci, streptococci and staphylococci. If the drug is used, it should be given in sufficient quantities to produce results or not at all. If the patient does not respond to one form of the drug, it is well to substitute one of the others. Our general rule for dosage is to give during the twenty-four hour period an amount totaling slightly less than one grain (0.06 gm.) per pound of body weight up to 90 pounds (41 kg.). During the first twenty-four hour period, we double, triple or quadruple the amount for the first two or three doses, depending on the severity of the infection and the type of patient. It is, of course, essential to watch the urine and blood carefully. At first a daily blood count is taken; later, if no bad effects are observed, the interval is lengthened to once in two days while the drug is being taken, with an additional count one week after it has been discontinued.

When laboratory work is unavailable because of inaccessible location or in time of war, the following points, as stated by Long,[8] should be watched:

First, if there is any history of toxic reaction in any previous therapy with these drugs, it must be remembered that there will probably be a second, earlier and more severe reaction. In these cases a small test dose must be given and the reaction closely watched.

Second, the patient should be seen daily and observations made for the following toxic signs:

1. Body aching, headache or malaise (toxic).
2. Sclera observed for jaundice (hepatic involvement).
3. Mucous membrane examined for pallor (anemia).
4. Skin examined for rashes (more severe toxemia).
5. Temperature and chills (more severe toxemia).
6. Urine should be *measured* and observed for blood (in order to anticipate anuria and kidney congestion).

By observation of the above, all toxic symptoms may be anticipated

excepting acute leukopenia; but no death has been reported during the first twelve days of treatment due to disturbances of the white blood cells.

The introduction of sulfanilamide directly into the sinuses and ears is still in the experimental stage.

Chemotherapy has unquestionably added greatly to the confidence of physicians in their ability to conquer acute otitis media, mastoiditis and fulminating sinusitis. We have always been apprehensive of meningitis as long as the ears and sinuses continued to discharge. In the twenty-five years prior to 1936, only 76 recoveries from streptococcic meningitis were reported in the literature; since 1936, more than 200 recoveries have been reported and mortality has dropped from 97 per cent to less than 35 per cent, and will drop still lower.[9] This is a great comfort and a signal achievement. Yet one should be ever mindful of the fact that chemotherapy when used in ear and nose infections so obscures the clinical picture that there is an increased danger of the unheralded sudden onset of grave complications, such as meningitis and osteomyelitis, and that under the influence of these drugs all the symptoms of mastoiditis and sinusitis may disappear while the lesion is actually spreading.

REFERENCES

1. Bowers, W. C. Treatment of sinusitis, *Virginia M. Monthly*, 1940, *67*:660; *West Virginia M. J.*, 1940, *36*:489.
2. Ballance, C. A. *Essays on the surgery of the temporal bone.* London, Macmillan, 1919, v. *2*, p. 426.
3. Heetderks, D. R. The reaction of normal nasal mucous membrane, *Am. J. M. Sc.*, 1927, *174*:231.
4. Hansel, F. K. *Allergy of the nose and paranasal sinuses.* St. Louis, Mosby, 1936.
5. Hoople, G. D. Non-surgical treatment of disease of the nose and pharynx, *Ann. Otol., Rhin. & Laryng.*, 1939, *48*:73.
6. Bowers, W. C. Observations on 793 cases of acute purulent otitis media with chemotherapy in 396 cases, *J. A. M. A.*, 1940, *115*:178.
7. Lyons, C. and Ganz, R. N. Clinical objectives in the chemotherapy of hemolytic streptococcic infections, *Laryngoscope*, 1940, *50*:756.
8. Long, P. H. *et al.* The toxic manifestation of sulfanilamide and its derivatives, *J. A. M. A.*, 1940, *115*:364.
9. Anderson, E. D. Hemolytic streptococcus meningitis, *J. A. M. A.*, 1937, *108*:1591.

A CRITICAL EVALUATION OF THE RESULTS OF ROUTINE CONSERVATIVE TREATMENT OF SYPHILIS*

HAROLD THOMAS HYMAN

THE SCOPE OF THE SYPHILIS PROBLEM IN THE UNITED STATES

In a recent survey,[1] routine blood tests gave serological evidences of syphilis in forty-four of every thousand American citizens. If these figures accurately depict the national situation, approximately 6,000,000 of our 130,000,000 citizens have been infected with lues. Of the 6,000,000 syphilitics, one half million are newly reported annually.[1]

Cardiovascular syphilis[1] accounts for 40,000 deaths each year. The domiciliary care of patients with dementia paralytica costs $31,000,000 annually.[1] An additional $10,000,000 is spent per annum for pensions and the care of the syphilitic blind.[1] Before the advent of the National Campaign for the Control of Syphilis, more than 60,000 syphilitic babies[1] were born annually within our borders.

The prevention and treatment of syphilis are formidable problems with widespread individual, communal and national consequences.

THE INDIVIDUAL AND THE SYPHILIS PROBLEM

The venereal diseases have been widely publicized in the lay press and over the air waves. This dissemination of medical information has marked a signal accomplishment in public health education. It has also given rise to considerable "syphilophobia" and certain misconceptions concerning the disease and its management. The Wassermann-negative members of the community scrutinize suspiciously their compatriots as possible integers in the moiety that makes up the Wassermann-positive portion of our population. The Wassermann-positive citizens view the future with dread, believing (1) that they are an infectious menace to the community and (2) that untreated, they face cardiovascular disease, blindness or insanity. Treated, they are told without adequate qualification, that "syphilis is curable."

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Reasons for the Present Survey

At the present time we are engaged in a national emergency. Our citizenry is being mobilized for service in the armed forces and in industry. It is a time when a national program for the control of syphilis may be instituted with a great prospect of significant achievement.

Simultaneously, the medical profession has been given a new form of attack[2, 3, 4] aimed at the treatment and possible eradication of syphilis. Massive dose chemotherapy by the intravenous drip method[5] gives promise of a high incidence of curability with a low, but definite, treatment hazard. During the period of the five days of active treatment, the patient is institutionalized and removed from contact with the community.

Preliminary to a discussion of the national program for the control of syphilis, it has seemed desirable to survey critically the results of the routine treatment of syphilis by conservative methods. In the light of these data, the relative risks and possible benefits of the more radical treatment may be measured, at a later time.

The Establishment of a Therapeutic Index Under Laboratory Conditions

Under the ideal conditions that exist in the laboratory, it is relatively simple to establish the therapeutic index of any specific drug that might be used in the treatment of a given infection.

Healthy standard animals are inoculated, under constant and supervised conditions, with a single strain and a uniform dose of the pathogen. Specific therapy is withheld from a "control" group, so that the incidence of "spontaneous cure" may be estimated. The remainder of the infected animals, under otherwise constant conditions, receive varying doses of the specific chemotherapeutic agent.

Toxicity is determined by (1) the sacrifice, at varying intervals, of treated animals, (2) the observations of the non-fatal complications in the survivors, and (3) autopsy of those who have succumbed to the lethal effect of the drug ("treatment deaths").

The therapeutic efficacy of the drug is estimated by a comparison of the recovery rate in the treated and controlled group.

The therapeutic index is gauged by balancing treatment risk against therapeutic efficacy.

The Variables in Clinical Chemotherapy

Clinical chemotherapy presents a much more intricate problem. It involves many variables relative to (1) the host, (2) the parasite, (3) the circumstances of the host-parasite interaction, (4) the therapeutic variables relative to time-dose factors, (5) the individual variations in the absorption, concentration or excretion of the drug, and (6) the social and economic costs and implications of therapy.

The Variables in the Chemotherapy of Syphilis

More concretely, the discussion which follows deals with the factors that must, of necessity, be evaluated in the estimation of the accomplishments of chemotherapy of syphilis by current conservative methods. The variables include (1) those relative to the individual patient (age, sex, color); (2) those pertinent to the strain and dose of the specific spirochete; (3) those incidental to the host-parasite inter-relationship, specifically with regard to morbidity, mortality and the spontaneous course of untreated syphilis; (4) those referable to the stage of the disease when therapy is instituted; (5) those referable to the nature, preparation and dose of the therapeutic agent or agents that are employed; (6) those pertaining to the presentation of statistics.

1. THE HOST

Congenital syphilis in infants is commonly fatal (Jeans and Cooke[6]).

Acquired syphilis in the prepubescent or elderly patient is prone to be most florid in its manifestations (Fournier[7]).

Women more frequently have asymptomatic infections than men.[8] Pregnancy favors the production of asymptomatic infection.[9]

Race and color alter the course of syphilis. The negro is more apt to develop cardiovascular lues.[10]

Amongst the variables pertinent to the host, syphilis may vary with age, sex and color.

2. THE PARASITE

Little is known concerning variations in the virulence of strains of spirochetes. However, the quantity of the inoculum may determine the clinical manifestations. Asymptomatic infection[11] may be induced, in the rabbit, by decreasing the amount of inoculum to a point where demonstrable lesions do not occur.

3. THE HOST-PARASITE INTER-RELATIONSHIP

The host-parasite inter-relationship is concerned with the problems of virulence, resistance and immunity. The ledger that scores the results of the conflict may be concerned with: (A) morbidity; (B) mortality; (C) the spontaneous cure of untreated syphilis.

(A) *Morbidity of Early Syphilis*

The morbidity and mortality of treated and untreated syphilis are difficult to estimate. Russell[1] has stated that 16.9 per cent of patients with untreated syphilis develop symptomatic neurosyphilis. Another 3.4 per cent develop cardiovascular syphilis. The morbidity for the disease from these two complications alone is thus slightly in excess of 20 per cent.

These figures may be compared with the data obtained by Bruusgaard[12] who attempted to learn the further course of 2181 untreated patients afflicted with primary or secondary syphilis. Bruusgaard traced 473 or 22 per cent of these patients. Of the 309 living individuals, only 35 per cent had clinical evidences of syphilis. Of 164 patients who died, for whatever reason, only 49 or 30 per cent died of syphilis.

(B) *Mortality of Early Syphilis*

Other than in congenital syphilis, immediate death from syphilis does not occur, at the present time.

The late mortality, in the Bruusgaard series, approximated 30 per cent of deaths caused directly by the ancient luetic infection.

(C) *The Spontaneous "Cure" of Early Syphilis*

It has been indicated above that but one-third of the syphilitics suffer from clinical lues. What is the fate of the remaining two-thirds? Is it possible for the host-parasite conflict to go on to a stalemate, the serology remaining positive and the patient clinically well? Is it possible for the host to triumph, the parasite to be vanquished, and the patient to undergo spontaneous cure with negativity of blood tests?

Sowder[13] has recently earned the gratitude of all students of syphilis by his survey of the Bruusgaard material. These data, may with profit, be briefly reviewed.

Under the aegis of Boeck who believed that the then-available specifics (potassium iodide and mercury) interfered with the host-parasite

relationship, specific therapy was withheld from his patients with early syphilis during the twenty year period from 1891 to 1910. In 1929, Bruusgaard reported on his efforts to contact the original 2181 patients included in this untreated group.

Information was obtained of 473 persons (22 per cent). Three hundred and nine of the patients were living. One hundred and sixty-four had died. Amongst the 309 living, 110 (35 per cent) had evidences of clinical syphilis. Sixty-eight (22 per cent) were clinically well with positive blood findings. One hundred and thirty-two (43 per cent) were clinically well with negative blood tests. Thus, the total clinically well, including the serologically positive group, was 200 patients or 65 per cent.

The analysis of 164 deaths reveals that 49 (30 per cent) died of syphilis. The remaining 70 per cent died of pulmonary tuberculosis, cancer, tumor or other causes.

Thus, of the 473 patients, living and dead, approximately one-third suffered from or died of syphilis. The remaining two-thirds were either clinically well or succumbed from other causes.

Sowder ably discusses the factors of selection. The baffling problem is the fate of the lost 1708 patients (78 per cent). Sowder concludes, with seeming justice, that the direction of the selection has been to exaggerate the gravity of the disease rather than to minimize it. The smaller group of followed cases included all or nearly all of the original patients who developed neurosyphilis and cardiovascular syphilis, as well as those who died of the disease. The larger group of 78 per cent, who were not followed, included few with neurosyphilis, cardiovascular or visceral syphilis, and few who succumbed to the disease. It is reasonable to assume that the "lost" group contained a relatively larger number of those who were clinically and serologically well. The reported group was probably weighted with the graver manifestations.

Employing, as a yardstick, the experience of Bruusgaard, the efficacy of any specific therapeutic measure must be one which will produce favorable results in excess of the 66 per cent expected "cure" rate of the spontaneous course of the disease.

(D) *The Spontaneous Course of Late Syphilis*

Supplementing the Bruusgaard studies, the Coöperative Clinical Group[14] has hypothecated the spontaneous course in untreated latent

syphilis. According to these prognostications, 25 to 35 per cent of the patients will go on to spontaneous "cure." An additional 25 to 35 per cent will be clinically well but serologically positive. The remaining 50 to 30 per cent will suffer from symptomatic syphilis including benign and late cardiovascular lues, neurosyphilis and visceral syphilis.

Specific treatment must appreciably transcend these results, if the therapeutic effort is to be justified.

4. VARIABLES RELATIVE TO TREATMENT

The evaluation of therapy in syphilis has already been shown to be modified by variables referable to the host and the host-parasite relationship. To these, must be added the variables dependent upon treatment.

The modern treatment of syphilis (excluding syphilis of the nervous system) is carried out with three of the heavy metals: arsenic, mercury and bismuth. Each of the heavy metals may be administered by several routes, employing several preparations. For the most part, arsenical therapy is given intravenously, and the arsphenamines and arsen-oxide are the preparations of choice. Bismuth is given orally or by intramuscular injection. Mercury may be given by inunction, by mouth, by intramuscular or occasionally, by intravenous injection.

The drugs may be given alone or in combination.

Treatment schedules agree in these respects:

1. The patient is given ambulatory treatment with divided doses.
2. The course of therapy, to be effectual, must be carried out for no less than a year, more often for two years, with an average of eighteen months or more, even under the most favorable circumstances.

Certain types of conventional routine treatment of syphilis may be recognized:

1. *Irregular treatment*, as the name implies, indicates that the patient has received spasmodic injections at such times as he has appeared at the clinic.
2. *Intermittent treatment* is accomplished by alternating a series of injections of arsenic and bismuth or mercury, followed by periods of rest.
3. *Continuous treatment* provides for alternation of courses of arsphenamine and courses of bismuth or mercury. Either of the latter overlaps the last arsenic injections of the previous series and the first arsenic injections of the succeeding series.

4. The "*best available conventional method of treatment*," as practiced by Moore, provides for continuous treatment as above and continued treatment.
5. *Continuous alternating* or *concurrent standard treatment* consists of at least thirty injections of an arsenical and at least forty injections of a heavy metal without any interruptions greater than one month. (U.S.P. H.S.)

Thus, a classical schema, such as proposed by Cole[15] for the treatment of early syphilis, calls for eleven injections of an arsenical in the first ten weeks, followed by six doses of bismuth at weekly intervals; another group of ten arsenicals, followed by eight bismuths; a third series of ten arsenicals followed by a third series of ten bismuths; a fourth series of ten arsenicals and ten bismuths.

The total span of therapy thus occupies seventy-five weeks. The patient receives no treatment from the seventy-fifth to the one hundred and third week, and then returns for a complete check-up. The continuous treatment is then continued, if necessary ("best available conventional method").

In latent syphilis, the Moore plan[16] (as carried out at the Vanderbilt University Hospital Syphilis Clinic) is initiated by three weekly doses of bismuth, followed by eight weekly doses of the arsenical; a second series of eight weekly doses of arsenic followed by twelve weekly doses of bismuth; a third series of eight arsenicals and then twelve bismuths. There then follows a rest period from the fifty-eighth to the sixty-ninth weeks. This is succeeded by twelve weekly doses of bismuth; a rest period from the eighty-second to the ninety-third weeks, and another series of twelve weekly bismuth injections which carries through to the one hundred and fifth week, or two years.

Thus, the treatment systems of syphilis vary widely from the haphazard, irregular type through the intermittent form up to the highly regimented continuous and continued methods, as practiced by the best syphilologists.

Results of Various Types of Therapy in Early Syphilis

Omitting from consideration, for the time being, all factors other than the type of treatment, the efficacy of each of these methods has been discussed most recently by Padget.[17] Reporting from Johns Hopkins Hospital, Padget selected, from approximately 6000 individuals with

early syphilis, a group of 551 patients who "had been completely re-examined five years or more after the termination of the original treatment for early syphilis." The outcome of the remaining 5449 is not discussed.

(A) *Spontaneous Course*

In the Padget series of 551 patients, 17 received no treatment and, of these, 35 per cent were clinically and serologically clear. One additional patient (5.9 per cent) was clinically well but serologically positive. Thus, of the untreated group, over 40 per cent had no clinical manifestations of the disease.

(B) *Intermittent or Irregular Treatment*

Two hundred and eighty-eight patients received intermittent or irregular treatment. Approximately 50 per cent of these were cured. Another 20 per cent were clinically well but serologically positive. The total of satisfactory cases approximated 70 per cent.

The outcome of therapy in this type of management led Padget to say: "In view of this essential uselessness of grossly irregular treatment in preventing the development of crippling late lesions of syphilis in the individual and its effect in the prolongation of the potential period of infectious relapse, is there any justification for the expenditure of the relatively large amount of effort which may be required to get an occasional treatment into an essentially uncoöperative patient? Is it perhaps not only permissible, but actually desirable, to allow such patients to go their way unmolested once they have demonstrated their unwillingness to coöperate? It is interesting that for entirely different reasons this point of view which prevails in Great Britain has recently been warmly supported by Harrison," and again, "The palpable inferiority of irregular and intermittent treatment strongly suggests that, if continuous treatment cannot be given, no treatment is the desideratum."

(C) *Continuous Treatment*

Continuous treatment was accomplished by 246 of Padget's group of 551 patients. Of these, it is reported that 83.4 per cent were cured. An additional 8.5 were clinically well, though serologically positive. Thus, approximately 92 per cent had a satisfactory response and but 8 per cent were suffering from infection.

(D) *Continuous and Continued Treatment*

Of the last group of 246 patients receiving treatment, 155 patients not only received continuous treatment but also continued their treatment. It is to this group that Moore refers when he speaks of the "best available conventional methods of treatment." In this small group (which constitutes 2.5 per cent of those who originally entered the clinic) 90 per cent are cured and another 5 per cent are clinically well but serologically positive, making a total of 95 per cent of satisfactory results.

In the Padget series, of selected cases of early syphilis, dependent wholly upon the system of therapy, the results vary between the "palpable inferiority" of the irregular and intermittent treatment, and the "highly satisfactory results" of the "best available conventional methods of treatment." The latter group constituted 28 per cent of the selected series, which made up 2.5 per cent of the original 6000 patients. It is possible that some of the unreported cases received optimum therapy, but these records are not included in the present report.

Cases Holding With Conventional Treatment

The first problem in the mass attack on syphilis is the establishment of an optimum system of treatment. The next challenge is the practical execution of that therapy.

Minimal adequate treatment has been defined by the Public Health Service as the accomplishment of the intravenous injection of 20 doses of an arsenical and 20 doses of bismuth within the first year of treatment.

Russell[1] has recently attempted to determine the percentage of patients with early syphilis who succeed in receiving minimal adequate treatment. Reporting from the United States Public Health Service, Russell studied 6,807 patients. Eighty-four per cent received less than twenty treatments; 11 per cent received less than thirty, and but 1.4 per cent received forty or more treatments. Of a second group of 590 patients, 328 received "inadequate" treatment, and 191 patients received "less than standard treatment." Thus, a total of 519 or 90 per cent received inadequate or less than standard treatment, and but 10 per cent received adequate treatment.

In the United States as a whole, Russell estimates that 95 per cent of the patients with early syphilis received inadequate treatment by conventional methods.

5. CASE LOSS AND STATISTICS

In face of a formidable case loss in conventional therapy, how is the syphilologist to evaluate therapy? If treatment is started in 100 patients, the majority may be expected to disappear from observation and become case losses. Are these patients to be reported as failures? If statistics are presented in this way, the maximum number of "cures" even if it includes all of the faithful, cannot approach the expectancy of spontaneous "cure."

On the other hand, if the statistics are based upon the patients that are followed, the reported results ignore the "lost" patients and present a false picture of the efficacy of treatment.

Morgan inquires, "What of those who receive inadequate treatment?" and responds, "It has been clearly demonstrated that inadequate treatment often reacts unfavorably on the course of the disease. The data supplied by the Coöperative Clinical Group, indicates that 13 per cent of the patients inadequately treated, redevelop acute infectious lesions, whereas only 2.7 per cent who receive 20 or more injections experience such recurrence."

The evaluation of specific therapeutic measures must represent the results obtainable in a consecutive series of patients. Presentations should state the total number of patients who initiated therapy and the total number of patients who completed therapy.

Our national problem, in the treatment of syphilis, concerns itself with the management of every syphilitic, not with the smaller group who can and will undergo the sacrifices and requirements of routine conventional therapy.

6. VARIABLES REFERABLE TO THE STAGE OF THE DISEASE AT THE INITIATION OF TREATMENT

The final variables to be discussed relate to the stage of the disease at the time of the initiation of therapy.

(A) *In Early Syphilis*

All syphilologists are in agreement that optimum results are to be anticipated in the treatment of early syphilis (primary sero-negative, primary sero-positive, and secondary lues). Less favorable chemotherapeutic achievement is anticipated in early latent, visceral or late latent

syphilis. The consideration of neurosyphilis is omitted from the present discussion.

Concentrating upon the results in early syphilis, there are two methods of presenting the results of specific therapy. Thus, Moore states[18] that the "chance for cure in the various stages of early syphilis employing the best available present day treatment" is 100 per cent in sero-negative primary syphilis, 95 per cent in sero-positive primary syphilis, and 90 to 95 per cent in early secondary syphilis.

This "chance for cure" is to be compared with the actual figure as presented from the same clinic. This report[18] indicates that in 140 cases of sero-negative primary syphilis, satisfactory clinical outcome occurred in 71.4 per cent; in 274, with sero-positive syphilis, a satisfactory outcome occurred in 53.3 per cent; in 910, with early secondary syphilis, satisfactory results were obtained in 49.8 per cent.

Again, in the Padget series of sero-negative primary syphilis, the percentage of cure was 82; in sero-positive primary syphilis, the percentage was 55; in secondary syphilis, 68 per cent; whilst, in early latent syphilis, there were but 58 per cent cured.

Treating similar material with mapharsen, Chargin, Leifer and Rosenthal,[19] in 188 cases, report 84 per cent satisfactory results.

How can these various figures be conciliated? Reference to the previous section clarifies the Moore figures concerning the "chance for cure." By this is clearly meant, the "chance for cure" in those patients who completed continuous and continued treatment ("the best available present day treatment"). This type of therapy was achieved by 155 of the 551 patients reported by Padget, the whole group having been selected from a total of 6000 individuals who initiated therapy. More succinctly stated, the figures for "chance for cure" are based on the experiences of 2.5 per cent of the whole group. The remaining figures, stated in terms of the number of patients actively treated, are based not upon those who initiated therapy, but those who completed therapy and were adequately followed. In no instance, are the calculations based upon the total number of patients who suffered from primary or secondary infectious syphilis and who sought therapy by the routine, conservative method.

The Morbidity of Adequately Treated Early Syphilis

Against the achievements of specific therapy must be weighed the

morbidity and mortality of the disease, the morbidity and mortality resulting from therapy.

In his small group of followed cases Padget, whose splendid report may well serve as a model, reports 3.8 per cent of his patients with benign late syphilis; 4.5 per cent with cardiovascular syphilis; 12.3 per cent with neurosyphilis; 1.3 per cent with multiple late manifestations; and a single patient who was treatment resistant.

Thus, the morbidity from the disease in these well treated and well followed patients totalled 19.4 per cent.

The mortality in the treated series showed that 1.8 per cent of the adequately treated patients died of syphilis (three from aortic regurgitation and seven from general paresis).

It is unfortunate that we are not in possession of the statistics concerning the morbidity and mortality in the unreported patients who began therapy. One may only speculate as to the circumstances. Sowder has, with justice, intimated that the "lost" group in the Bruusgaard series probably showed less evidences of the ravages of syphilis than the group that was followed, i.e., the followed group was weighted with the more serious complications. It would seem reasonable to assume that the opposite conclusion held in the unreported group in the Padget series. These patients received inadequate treatment and their roster must be weighted with the graver manifestations of the disease.

To the morbidity and mortality of the disease itself must be added the morbidity and mortality incident to treatment. In the Padget series, forty-three patients sustained serious reaction to treatment (8 per cent). Nineteen of the group had arsphenamine dermatitis; eighteen had post-arsphenamine jaundice; two had both complications; one patient had a blood dyscrasia. The others were scattering. There were no reported treatment deaths.

What of the treatment morbidity and mortality in the lapsed group? Is it possible that some of the patients who failed to return suffered reactions that discouraged them from continuing therapy? Is it possible that treatment deaths (which commonly seem to occur in routine treatment once in three hundred to once in four hundred patients) may have occurred in the lapsed series and that such patients are classified as case losses? The question is posed because of our experience that the serious and fatal arsenical complications often make their way to another institution rather than to the ambulatory treatment clinic where therapy was administered.

TABLE I

ESTIMATE OF THE PROBABLE OUTCOME OF LATENT SYPHILIS
(Moore, Bruusgaard, and C. C. G.)

	"Cure"	Latent Infection	Late Syphilis (Skin, Mucosal, Osseous)	C-V Syphilis	Neuro-Syphilis	Other Visceral Syphilis
	per cent	per cent	per cent	per cent	per cent	per cent
Untreated	25-35	25-35	10-15	10-15	1-2.0	0.5-1
Adequately treated early syphilis	70-80	20-25	2-5	2-5	1-2	0.5-1
Adequately treated late syphilis	60-70	25-35*	1.6	1.6	1.6	

* "Wassermann fast"

(B) Late Syphilis

The evaluation of the efficacy of therapy becomes increasingly more complicated in late syphilis. Morgan[16] has presented a table in which there is estimated the probable outcome of latent syphilis, as based upon the experiences of Moore, Bruusgaard and the Coöperative Clinical Group. This chart is reproduced herewith (Table I).

The critical reader may ponder upon the relationship that exists between these estimated results, and the actual figures in terms of patients treated. How can these prognostications be conciliated with the citation by Morgan of Moore's statement that "about 35 per cent of all patients with late latent syphilis are persistently Wassermann-positive under any form of treatment." If this be accepted, treatment-results in latent syphilis must more nearly approach the Bruusgaard figures for spontaneous cure than the "chance for cure of early syphilis, employing the best available present day treatment."

Summary

1. Critical evaluation of the results of the routine conservative treatment of syphilis requires a consideration of the modifications that arise due to the interpolation of several variables.
2. The course of syphilis may vary with the age, sex and race of the host.

3. The course of the disease may vary, dependent upon the quantity of the inoculum.
4. Studies of the "spontaneous" course of early syphilis indicate that one patient in three will suffer clinical manifestations of the disease.
5. The "spontaneous" course of early syphilis tends to "cure" in approximately 43 per cent of all patients, and an additional 22 per cent will remain clinically well with positive serology. Thus, two patients in three, afflicted with early syphilis, may be expected to live their lives and eventually succumb without clinical manifestation of the infection.
6. The incidence of expected "spontaneous cure" of late syphilis approximates but does not quite equal the anticipated incidence in early syphilis.
7. The results of therapy in syphilis vary with the treatment schedules. All schedules agree in that the patient is given ambulatory treatment, with divided doses, over the course of a long period of time, averaging perhaps in excess of eighteen months, even under the most favorable circumstances.
8. The protracted nature of the therapy results in a "case loss" approximating 80 per cent under optimal conditions, and exceeding 90 per cent in a nation-wide survey.
9. Those patients who make up the larger group of "case loss," have necessarily received inadequate treatment. The best authorities agree that inadequate treatment often reacts unfavorably on the course of the disease. The "case losses" make up the reservoir of infectious syphilis.
10. Under optimal conditions in the well-organized clinic, the minority of those who have initiated therapy receive minimal adequate treatment. Under nation-wide conditions, the number who receive 20-20, (20 injections of arsenic intravenously and 20 injections of the heavy metals intramuscularly over the span of a single year) is perhaps in the vicinity of 5 per cent.
11. Those who complete adequate minimal treatment receive courses by several methods, i.e., the irregular, the intermittent, the continuous or the continuous and continued, the last named constituting the "best available conventional method of treatment."
12. Syphilologists state of irregular treatment, that it is "essentially useless."

13. Of irregular and intermittent treatment, it is stated that their "palpable inferiority strongly suggests that if continuous treatment cannot be given, no treatment is the desideratum."
14. As a positive contribution to the specific chemotherapy of syphilis, there remains only the continuous form of treatment.
15. Only a small percentage of patients initiate therapy and remain under active treatment until the satisfactory continuous course of therapy has been completed.
16. So far as can be mathematically proven, specific chemotherapy exceeds the result of the spontaneous course of the disease only in the treatment of early syphilis by the continuous method. The treatment-results reported in latent and visceral syphilis seem not greatly different from the "spontaneous cures" experienced by the Bruusgaard patients from whom all specific therapy was withheld.
17. The great triumph of specific chemotherapy in syphilis seems sharply limited to those patients with early syphilis (constituting perhaps 16 per cent of Wassermann-positive individuals) who have persisted through continuous and continued forms of therapy (5 per cent of those who initiate therapy).
18. The more glowing reports of specific chemotherapy in syphilis are based upon "expectation of cure" rather than upon actual statistics. The available statistics that are published do not consider the total number of patients that initiated therapy. They ignore the majority of infected individuals who have lapsed from therapy.
19. The statement, "syphilis is curable," requires many qualifications.

Conclusions

The present day management of syphilis by the conventional methods of treatment is pitifully inadequate for our national program for the prevention and treatment of this dread disease.

The attack against syphilis must realistically recognize these fundamental tenets:

1. Treatment must be focused upon early syphilis.
2. The completion of therapy for early syphilis must be mandatory, not optional.
3. During the infectious stage, the patient must be institutionalized.
4. Practically, to accomplish these aims, the intensity of therapy must be increased, so that the duration of treatment is sharply decreased.

5. The results of specific therapy must transcend the expectancy of spontaneous cure.
6. The computation of results must be based on the total number of patients initiating treatment.

REFERENCES

1. Russell, A. E. Syphilis case finding in industry, *J.A.M.A.*, 1940, *114:*1321.
2. Chargin, L., Leifer, W., and Hyman, H. T. Studies of velocity and response to intravenous injections: application of intravenous drip method to chemotherapy as illustrated by massive doses of arsphenamine in the treatment of early syphilis, *J.A.M.A.*, 1935, *104:*878.
3. Hyman, H. T., Chargin, L., Rice, J. L., and Leifer, W. Massive dose chemotherapy of early syphilis by the intravenous drip method, *J.A.M.A.*, 1939, *113:*1208.
4. Hyman, H. T., Chargin, L., and Leifer, W. Massive dose arsenotherapy of syphilis by the intravenous drip method, *Am. J. Syph., Gon. & Ven. Dis.*, 1939, *23:*685.
5. Hyman, H. T. Massive dose chemotherapy by the intravenous drip method, *Bull. New York Acad. Med.*, 1941, *17:* 135.
6. Jeans, P. C. and Cooke, J. V. *Prepubescent syphilis.* New York, D. Appleton & Company, 1930.
7. Fournier, J. A. *Traité de la syphilis.* Paris, Rueff, 1899.
8. Moore, J. E. *et al.* Syphilis in women, *Ven. Dis. Inform.*, 1932, *13:*317.
9. Moore, J. E. Syphilis in pregnancy, *Bull. Johns Hopkins Hosp.*, 1923, *34:*89.
10. Turner, T. B. The race and sex distribution of lesions of syphilis in ten thousand cases, *Bull. Johns Hopkins Hosp.*, 1930, *46:*159.
11. Morgan, H. J., and Vryonis, G. P. The inoculum in syphilis, *Am. J. Syph., Gon., and Ven. Dis.*, 1938, *22:*462.
12. Bruusgaard, E. Ueber des Schicksal der nicht spezifisch behandelten luetiker, *Arch. f. Dermat. u. Syph.*, 1929, *157:* 309.
13. Sowder, W. T. An interpretation of Bruusgaard's paper on the fate of untreated syphilitics, *Am. J. Syph., Gon. & Ven. Dis.*, 1940, *24:*684.
14. Moore, J. E. *et al.* Spontaneous course of untreated latent syphilis, *Ven. Dis. Inform.*, 1932, *13:*351.
15. Cole, H. N. The use of antisyphilitic remedies, *J.A.M.A.*, 1936, *107:*2123.
16. Morgan, H. Syphilis, in *Modern medical therapy in general practice,* ed. by D. P. Barr. Baltimore, Williams and Wilkins, 1940.
17. Padget, P. Long-term results in the treatment of early syphilis, *Am. J. Syph., Gon. & Ven. Dis.*, 1940, *24:*692.
18. Moore. Quoted by Morgan (16).
19. Chargin, L., Leifer, W. and Rosenthal, T. Mapharsen in the treatment of early syphilis: comparison of results in one hundred eighty-eight cases with those of the cooperative clinical group, *Arch. Dermat. & Syph.*, 1939, *40:*208.

DEATHS OF FELLOWS

BANTING, SIR FREDERICK GRANT: 205 Rosedale Heights Drive, Toronto, Ont., Canada; born in Alliston, Ont., November 14, 1891; killed in an airplane accident near Musgrave Harbor, Newfoundland, February 21, 1941; received from the University of Toronto, Faculty of Medicine, the degree M.B. in 1916 and M.D. in 1922; elected an Honorary Fellow of the Academy March 2, 1933.

Dr. Banting was resident surgeon to the Hospital for Sick Children in Toronto, Ont. 1919-20 and part-time assistant in physiology at the Western University Faculty of Medicine, London, Ont. 1920-21. In May 1921, he commenced research on the internal secretion of the pancreas at the University of Toronto, Ont. At that institution, he was also lecturer on pharmacology, 1921-22, and senior demonstrator in medicine, 1922-23. Since 1923 he was professor of medical research in the Banting and Best Department of Medical Research, a chair which was established by the University of Toronto in recognition of his work on insulin. He was honorary consulting physician to the Toronto General and Toronto Western Hospitals.

In 1922 he was awarded the Starr Gold Medal and the George Armstrong Peters Prize and in 1923 the Charles Mickle Fellowship and the Reeve Prize, all of the University of Toronto. In 1923 he shared the Nobel Prize with Dr. J. J. R. MacLeod. In 1924 he was awarded the John Scott Medal by the city of Philadelphia and received a life annuity of $7,500 from the parliament of Canada; in 1924 he was awarded the Rosenberger Gold Medal by the University of Chicago; in 1927 the Cameron Prize by the University of Edinburgh; in 1931 the Flavelle Medal by the Royal Society of Canada; in 1934 the Apothecaries' Medal of London; in 1936 the F. N. G. Starr Gold Medal by the Canadian Medical Association.

Dr. Banting was knighted a Commander of the Civil Division of the Order of the British Empire in 1934. He was a licentiate of the Royal College of Physicians, member of the Royal College of Surgeons, fellow of the American College of Physicians, fellow of the Royal College of Surgeons of England, fellow of the Royal College of Surgeons of London, fellow of the Royal College of Surgeons of Canada, fellow of the Royal Society and fellow of the Royal College of Physicians. He was an honorary fellow of the Academy of Medicine of Toronto; honorary member of the Norwegian Medical Society in Oslo; foreign correspondent, Académie royale de médecine de Belgique; La Società mèdico-chirurgia de Bologna; corresponding member of the Royal Medical Society of Budapest; member of the Canadian Medical Association, American Society for Pharmacology and Experimental Therapeutics, British Physiological Society, Association of American Physicians, Canadian Chemical Association, American Association for Cancer Research and the Imperial German Academy of Natural Sciences.

For three years during the World War, Dr. Banting served with the Canadian Army Medical Corps, and he was again serving as a major in the medical corps of the Canadian Army at the time of his death. In 1918 he was awarded the Military Cross. He held honorary degrees from the University of Toronto, Queen's University, University of Western Ontario, Yale University and the University of the State of New York.

BURRETT, CLAUDE ADELBERT: 1 East 105 Street, New York City; born at North Greece, Monroe County, New York, July 13, 1878; died in New York City, March 3, 1941; graduated in medicine from the Cleveland Homeopathic Medical College in 1905; elected a Fellow of the Academy November 4, 1937.

Dr. Burrett was director of the pathogenic laboratory and instructor in toxicology at the University of Michigan College of Homeopathic Medicine, Ann Arbor, from 1905 to 1908; from 1908 to 1913, assistant professor of genito-urinary surgery, der-

matology and electrotherapeutics; and from 1913 to 1914, professor of surgery and genito-urinary surgery. At the Ohio State University College of Homeopathic Medicine, Columbus, Dr. Burrett was professor of surgery and acting dean from 1914 to 1915, and dean and professor of surgery from 1915 to 1922. At the New York Medical College, Flower and Fifth Avenue Hospitals, formerly known as the New York Homeopathic Medical College and Flower Hospital, he was dean, professor of surgery and director from 1925 to 1939, and its president since 1939.

Dr. Burrett was a Fellow and a former member of the Board of Governors of the American College of Surgeons, a member of the Medical Council of the State Board of Regents, a trustee of Syracuse University, a Fellow of the American Medical Association and a member of the State and County Medical Societies.

During the World War, Dr. Burrett was surgeon to the student army training corps at Ohio State University and a member of the medical division of the Ohio Defense Board.

CRAMP, WALTER CONCEMORE: 1001 Park Avenue, New York City; born in Hamilton, New York, April 12, 1878; died in New York City February 18, 1941; received from Colgate University the degree A.B. 1900, and D.Sc. 1923; graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1904; elected a Fellow of the Academy December 3, 1908.

Dr. Cramp had practiced surgery in New York City since 1904. He was assistant professor of surgery at Bellevue Medical School for six years and at one time was visiting surgeon to the Willard Parker, St. Francis, and Bellevue Hospitals and the Hospital for Joint Diseases. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a Trustee of Colgate University, and a member of the State and County Medical Societies.

MACPHEE, JOHN JOSEPH: 146 East 49 Street, New York City; born at St. Margaret, Prince Edward Island, Canada, July 8, 1860; died in New York City, February 18, 1941; graduated in medicine from the University of Vermont in 1890; elected a Fellow of the Academy December 7, 1905.

Dr. MacPhee was emeritus professor of neurology at the New York Post-Graduate Medical School, Columbia University; attending neurologist to the St. Francis Hospital and consulting neurologist to the Misericordia and Post-Graduate Hospitals, the Bronx Eye and Ear Infirmary, the Harlem Eye and Ear Infirmary, and St. John's Hospital at Long Island City. He was a Fellow of the American Medical Association, a member of the Association for Research in Nervous and Mental Disease, and a member of the State and County Medical Societies.

WENCKEBACH, KAREL FREDERIK: Vienna, Austria; born at The Hague, Holland, March 12, 1864; died in Vienna, November 11, 1940; elected an Honorary Fellow of the Academy March 2, 1933.

After receiving his medical degree from the University of Utrecht, Dr. Wenckebach was appointed in 1888 as assistant in the Institute of Zoology, and afterwards in the Department of Pathology and Normal Anatomy. In 1901 he was elected professor of internal medicine at Groningen, and from 1911 to 1914 he held the same post at the University of Strasbourg. He was then called to the chair of medicine at the University of Vienna, as professor of medical pathology and therapy, and was made emeritus professor of medicine in 1929. Throughout those years Wenckebach identified himself with progress in the study, pathological and clinical, of diseases of the heart and circulatory system, publishing many important contributions to cardiological knowledge between 1901 and 1932. For some years he edited, jointly with Drs. Falta and Jagic, the ***Wiener Archiv für innere Medizin.***

Dr. Wenckebach was an Honorary Fellow of the Royal College of Physicians and of the Royal Society of Medicine, and a Foreign Corresponding Member of the British Medical Association. He was noted as the founder of the science of electrocardiography and achieved fame as one of the first students in the study of the arhythmias of the heart.